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Jon W. Dudas

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Attorney Docket No.	RIB-014PR
First Named Inventor	Bhattacharjee

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TITLE OF THE INVENTION (280 characters max)

Bifunctional Heterocyclic Derivatives and Methods of Making and Using the Same

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒	Specification (*Number of Pages* 116)	☐	CD(s) (Number ____)
☐	Drawing(s) (*Number of Sheets* ____)	☒	Application Data Sheet
☒	Return Receipt Postcard	☐	Other *(specify)*:

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PATENT
Attorney Docket No. RIB-014PR

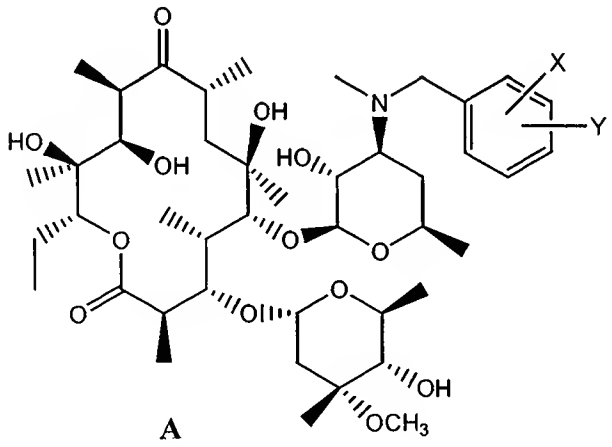
BIFUNCTIONAL HETEROCYCLIC DERIVATIVES AND METHODS OF MAKING AND USING THE SAME

FIELD OF THE INVENTION

The present invention relates generally to the field of anti-infective and anti-proliferative, agents. More particularly, the invention relates to a family of bifunctional heterocyclic compounds useful as such an agent.

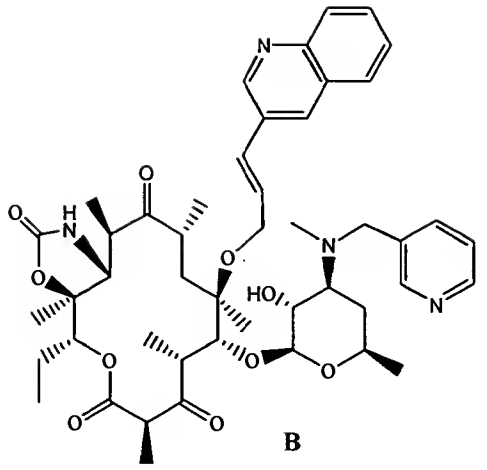
BACKGROUND

U.S. Patent No. 3,681,325 discloses N-benzyl derivatives of erythromycin having the general structure **A**, which are useful as antibacterial agents. International Publication No. WO 99/22722 discloses similar compounds useful for treating cancer and macular degeneration.



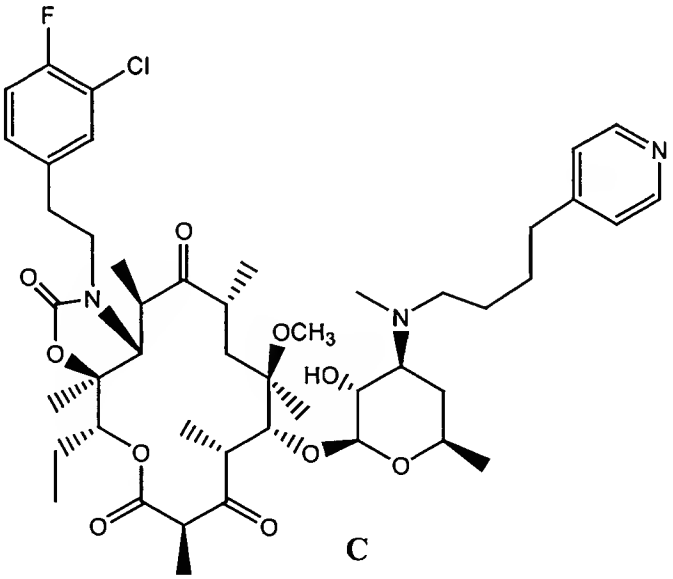
A

U.S. Patent No. 6,034,069 and International Publication No. WO 99/16779 disclose a series of 3'-N-modified 6-O-substituted erythromycin ketolide derivatives similar to compound **B**. Various aryl (represented by a 3-pyridyl group in **B**) and non-aryl groups were attached to the desosamine nitrogen atom.



B

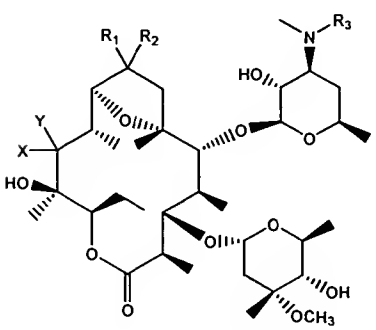
U.S. Patent Nos. 6,020,521 and 5,955,440 disclose macrolide derivatives similar to structure **C**. A wide range of aromatic and heteroaromatic groups were employed as substituents linked to the desosamine nitrogen atom. The compounds were claimed as antagonists of lutenizing hormone-releasing hormone.



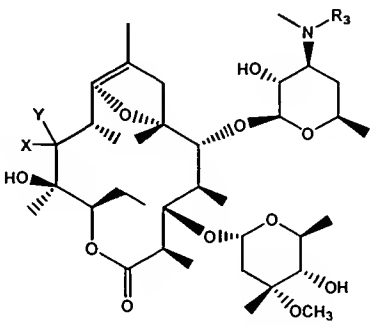
C

Compounds of structures **D**, **E**, and **F** were disclosed in *J. Med. Chem.* **1998**, *41*, 3402, International Publication Nos. WO 97/48713, WO 94/10185, WO 93/24509 and European Patent Nos. EP 0 215 355 B1 and EP 0 213 617 B1. Certain of the derivatives contained arylalkyl groups at the R_3 position on the desosamine nitrogen atom. The compounds stimulate

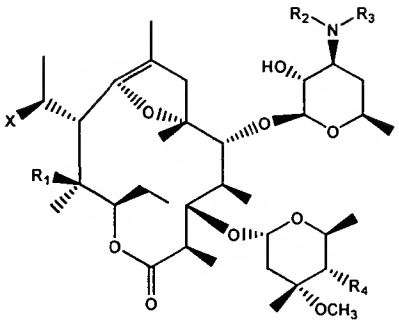
contractions of the gastrointestinal tract, and are claimed to be useful in treating diabetic gastroparesis and gastroesophageal reflux disease.



D: X,Y = H, OH; or =O

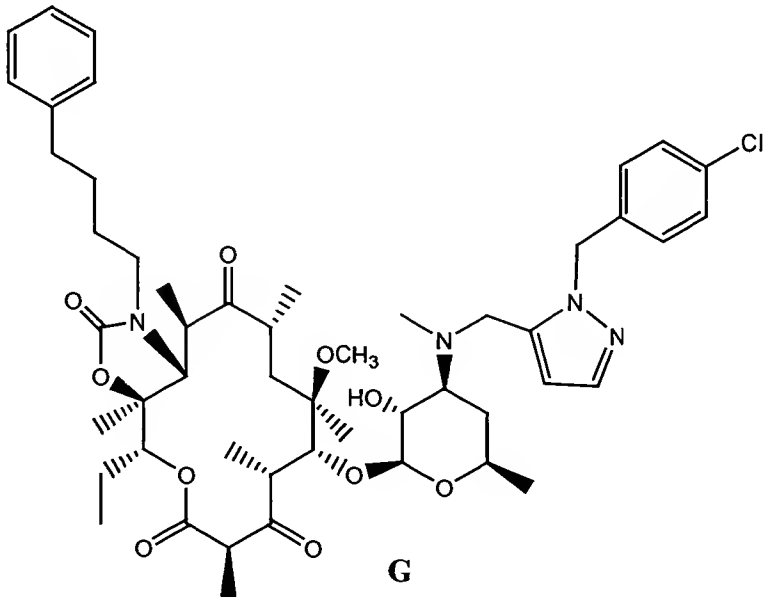


E: X,Y = H, OH; or =O



F

Compound **G** and related derivatives were disclosed in *Tetrahedron Letters* **2002**, *43*, 4171. The compounds were synthesized via reductive amination chemistry from the monomethylamine derived from the desosamine sugar portion of a ketolide intermediate and a variety of aromatic and heteroaromatic aldehydes. The compounds were described to be of interest as anti-bacterial agents, however, no biological activity data was reported.

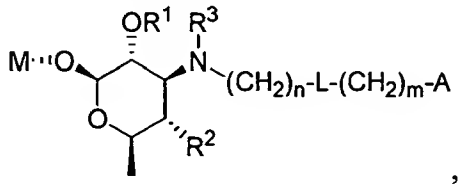


G

Notwithstanding the foregoing, there is still an ongoing need for new macrolide ring-containing anti-infective and anti-proliferative agents.

SUMMARY OF THE INVENTION

The invention provides a family of compounds useful as anti-infective agents and/or anti-proliferative agents, for example, chemotherapeutic agents, anti-microbial agents, anti-bacterial agents, anti-fungal agents, anti-parasitic agents, anti-viral agents, anti-inflammatory agents, and/or prokinetic (gastrointestinal modulatory) agents, having the formula:



,

or pharmaceutically acceptable salts, esters, or prodrugs thereof. In the formula, n and m independently are 0, 1, 2, 3, 4, 5, or 6. The variables M, R^1, R^2, R^3, L, and A can be selected from the respective groups of chemical moieties later defined in the detailed description.

In addition, the invention provides methods of synthesizing the foregoing compounds. Following synthesis, a therapeutically effective amount of one or more of the compounds may be formulated with a pharmaceutically acceptable carrier for administration to a mammal for use as an anti-cancer, anti-microbial, anti-biotic, anti-fungal, anti-parasitic or anti-viral agent, or to treat a proliferative disease, an inflammatory disease or a gastrointestinal motility disorder. Accordingly, the compounds or the formulations may be administered, for example, via oral, parenteral, or topical routes, to provide an effective amount of the compound to the mammal.

The foregoing and other aspects and embodiments of the invention may be more fully understood by reference to the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a family of compounds that can be used as anti-proliferative agents and/or anti-infective agents. The compounds may be used without limitation, for example, as anti-cancer, anti-microbial, anti-bacterial, anti-fungal, anti-parasitic and/or anti-viral agents. Further, the present invention provides a family of compounds that can be used without limitation as anti-inflammatory agents, for example, for use in treating chronic inflammatory airway diseases, and/or as prokinetic agents, for example, for use in treating gastrointestinal motility disorders such as gastroesophageal reflux disease, gastroparesis (diabetic and post surgical), irritable bowel syndrome, and constipation.

1. Definitions

For the purpose of the present invention, the following definitions have been used throughout.

The carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} defines the number of carbon atoms present from the integer "i" to the integer "j", inclusive. Thus, the term "C_{1-6} alkyl" refers to a straight chain, branched, or cyclic group having one to six carbon atoms, such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, and their isomeric forms, and cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "C_{2-6} alkenyl" refers to a straight chain, branched, or cyclic group having two to six carbon atoms and at least one double bond, such as, for example, ethenyl, propenyl, butenyl, pentenyl, pentdienyl, hexenyl, hexadienyl, and their isomeric forms, and cyclobutenyl, cyclopentenyl and cyclohexenyl.

The term "C_{2-6} alkynyl" refers to a straight chain or branched group having two to six carbon atoms and at least one triple bond, such as, for example, ethynyl, propynyl, butynyl, pentynyl, pentdiynyl, hexynyl, hexdiynyl, and their isomeric forms.

The term "C_{1-6} alkoxy" refers to an oxygen atom attached to an alkyl group having one to six carbon atoms, such as, for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, hexyloxy, and their isomeric forms.

The term "C_{1-6} alkylthio" refers to a sulfur atom attached to an alkyl group having one to six carbon atoms.

The term "C_{1-6} acyl" refers to a carbonyl group having an alkyl group of one to six carbon atoms, such as, for example, acetyl, propanyl, isopropanyl, butyl, and isobutyl.

The term "C_{1-6} alkoxycarbonyl" refers to an ester group having an alkyl group of one to six carbon atoms, such as, for example, acetate, and propanoate.

The terms "halo" or "halogen" refers to a fluorine atom, a chlorine atom, a bromine atom, and/or an iodine atom.

The term "hydroxy protecting group" refers to an easily removable group which is known in the art to protect a hydroxyl group against undesirable reactions during synthetic procedures and to be selectively removable. The use of hydroxy-protecting groups is well known in the art and many such protecting groups are known (see, for example, T.H. Greene and P.G.M. Wuts

(1999) PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, 3rd edition, John Wiley & Sons, New York). Examples of hydroxy protecting groups include, but are not limited to, acetate, methoxymethyl ether, methylthiomethyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, and acyl substituted with an aromatic group.

The terms "aryl" and "aromatic" refer to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, and indenyl.

The term "substituted aryl" refers to an aryl group, as defined herein, substituted by independent replacement of one or more of the hydrogen atoms thereon with substituents independently selected from lower alkyl, substituted lower alkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, acylamino, cyano, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. More specifically, the substituents may be F, Cl, Br, I, OH, NO_2, CN, C(O)-C_{1-6} alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-C_{1-6} alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C_{1-6} alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO_2-heteroaryl, $OCONH_2$, OCONH-C_{1-6} alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C_{1-6} alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-C_{1-6} alkyl, NHCONH-aryl, NHCONH-heteroaryl, SO_2-C_{1-6} alkyl, SO_2-aryl, SO_2-heteroaryl, SO_2NH_2, SO_2NH-C_{1-6} alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, C_{1-6} alkyl, C_{3-6} cycloalkyl, CF_3, CH_2CF_3, $CHCl_2$, CH_2OH, CH_2CH_2OH, CH_2NH_2, $CH_2SO_2CH_3$, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_{1-6} alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C_{1-3} alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_{1-6} alkyl-thio, or methylthiomethyl. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "heterocyclic" refers to a five to ten membered cyclic group containing one or more oxygen, nitrogen, or sulfur atoms. Heterocyclic groups include, for example, oxiranyl, aziridinyl, thiranyl, oxetanyl, azetidinyl, thietanyl, tetrahydrofuranyl, pyrrolininyl, tetrahydrothiophenyl, tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl, dioxanyl, morpholino, and piperazinyl.

The terms "heteroaryl" and "aromatic heterocyclic" refer to a five to ten membered cyclic aromatic group containing one or more oxygen, nitrogen, or sulfur atoms. The group may be

joined to the rest of the molecule via any of the ring atoms. Heteroaryl/heteroaromatic groups include, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, and isoquinolinyl.

The term "bicyclic aromatic heterocyclic" refers to a bicyclic aromatic ring system containing one or more oxygen, nitrogen, or sulfur atoms. Bicyclic heteroaromatic groups include, for example, indolyl, benzimidazolyl, benzofuranyl, quinolinyl, isoquinolinyl, and benzthiazolyl.

The terms "substituted heteroaryl" and "substituted heterocyclic" refer to a heteroaryl or heterocyclic group as defined herein, substituted by independent replacement of one or more of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO_2, CN, C(O)-C_{1-6} alkyl, C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-C_{1-6} alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C_{1-6} alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO_2-heteroaryl, $OCONH_2$, OCONH-C_{1-6} alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C_{1-6} alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-C_{1-6} alkyl, NHCONH-aryl, NHCONH-heteroaryl, SO_2-C_{1-6} alkyl, SO_2-aryl, SO_2-heteroaryl, SO_2NH2, SO_2NH-C_{1-6} alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, C_{1-6} alkyl, C_{3-6} cycloalkyl, CF_3, CH_2CF_3, $CHCl_2$, CH_2OH, CH_2CH_2OH, CH_2NH_2, $CH_2SO_2CH_3$, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_{1-6} alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C_{1-3} alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_{1-6} alkyl-thio, or methylthiomethyl.

The term "amine" refers to compounds having the formula $-NH_2$, -NH-, $-NHR^7$, $-NR^7-$, or $-NR^7R^8$ wherein R^7 and R^8 are independently selected from the group consisting of hydrogen, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group, wherein the C_{1-6} alkyl group, the C_{2-6} alkenyl group, and the C_{2-6} alkynyl group are optionally substituted with one or more substituents selected from the group consisting of halogen, an aryl group, a substituted aryl group, a heterocyclic group, a substituted heterocyclic group, $-OR^5$, and $-NR^9R^{10}$; wherein (a) R^5 is selected from the group consisting of hydrogen, a hydroxy protecting group, R^6, -V-W-R^6, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group, wherein (i) R^6 is selected from the group consisting of hydrogen, an aryl group, a substituted aryl group, a heterocyclic group, and a substituted heterocyclic group; (ii) V is selected from the group consisting of -C(O),

-C(O)O-, -C(O)NR^7-, or absent; (iii) W is a C_{1-6} alkyl group, a C_{2-6} alkenyl group, C_{2-6} alkynyl group, or absent; and (iv) the C_{1-6} alkyl group, the C_{2-6} alkenyl group, and the C_{2-6} alkynyl group are optionally substituted with one or more substituents selected from the group consisting of a halogen, an aryl group, a substituted aryl group, a heteroaryl group, a substituted heteroaryl group, –OR^6, -O-C_{1-6} alkyl group-R^6, -O-C_{2-6} alkenyl group-R^6, -O-C_{2-6} alkynyl group-R^6, and –NR^{7}R^8; and (b) R^9 and R^{10} are (i) independently selected from the group consisting of hydrogen, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group; or (ii) R^9 and R^{10} taken together with the nitrogen atom to which they are connected form a 3- to 7-membered ring, optionally containing one or more substituents selected from the group consisting of –O–, –NH–, -N(C_{1-6} alkyl group) –, –N(aryl)–, –N(heteroaryl)–, –S–, -S(O)–, –SO_2–, and –C(O)–.

The term "amide" refers to compounds having the formula –C(O)NH_2, –C(O)NH-, -C(O)NHR^7, -C(O)NR^7-, or -C(O)NHR^{7}R^8 wherein R^7 and R^8 are as described above.

The term "imine" refers to compounds having the formula –C(NH)- or –C(NR^7)- wherein R^7 is as described above.

The term "oxime" refers to compounds having the formula –C(NOH)- or –C(NOR^7)- wherein R^7 is as described above.

The term "sulfonamide" refers to compounds having the formula –SO_2NH-, -SO_2NH_2, -SO_2NR^7-, -SO_2NHR^7, or –SO_2NR^{7}R^8 wherein R^7 and R^8 are as described above.

The term "sulfoxide" refers to compounds having the formula –S(O)- or –S(O)R^7 wherein R^7 is as described above.

The term "sulfone" refers to compounds having the formula –SO_2-, –SO_2H or –SO_2R^7 wherein R^7 is as described above.

The term "sulfonyl ester" refers to compounds having the formula –SO_2O- or –SO_2OR^7 wherein R^7 is as described above.

The term "macrolide" refers to any compound possessing a 14- or 15-member macrocyclic ring, and derivatives thereof (such as keto, oxime, cyclic carbonate derivatives). These include, for example, compounds that are (or are synthetically derived from) known antibacterial agents including, but not limited to, erythromycin, clarithromycin, azithromycin, telithromycin, roxithromycin, pikromycin, flurithromycin, and dirithromycin.

The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and

lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in J. PHARM SCIENCES 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid, or by using other methods used in the art such as ion exchange.

Other pharmaceutically acceptable salts include, for example, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include, for example, sodium, lithium, potassium, calcium, and magnesium. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

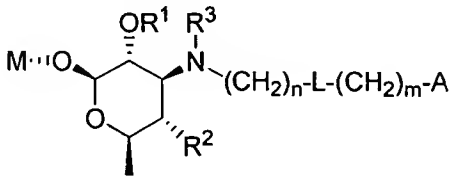
The term "pharmaceutically acceptable ester" refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates, and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the previously formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987.

Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions of the present invention also consist essentially of, or consist of, the recited components, and that the processes of the present invention also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, two or more steps or actions may be conducted simultaneously.

2. Compounds of the Invention

In one aspect, the invention provides compounds having the formula:



or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein

M is a 14- or 15-membered macrolide linked via a macrocyclic ring carbon atom;

R^1 and R^3 independently are hydrogen, a C_{1-6} alkyl group, or a C_{1-6} acyl group;

R^2 is hydrogen or $-OR^1$;

n and m independently are 0, 1, 2, 3, 4, 5, or 6;

L is

(a) a sulfonamide group;

(b) a 5- or 6-membered saturated, unsaturated or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms, and optionally substituted with one or more chemical moieties selected from the groups consisting of:

(i) a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; and a nitro group; and

(ii) a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; a sulfonyl ester group, and a 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms;

wherein each of the moieties of (b)(ii) immediately above optionally is substituted with one or more chemical moieties selected from the group consisting of: a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; a nitro group, a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; a sulfonyl ester group; and a 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms; or

(c) $-D_p-(CH_2)_r-$(5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms) $-(CH_2)_{r'}-D_{p'}-$,

wherein

(i) D is a C_2 alkenyl group; an oxygen atom; an amine group; an amide group; a sulfur atom; a sulfoxide group; a sulfone group; a sulfonyl ester group; sulfonamide group; a carbonyl group; an imine group; an oxime group; a thioketone group; or a 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms as described in (b) immediately above;

(ii) p and p' independently are 0 or 1;

(iii) r and r' independently are 0, 1, 2, 3, or 4; and

(iv) the 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms is as described in (b) immediately above;

A is (a) a phenyl group; (b) a bicyclic aromatic group containing up to ten carbon atoms; (c) a 5- or 6-membered aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms; or (d) a bicyclic aromatic heterocyclic group containing up to ten carbon atoms and one or more oxygen, nitrogen, and sulfur atoms,

wherein each of (a)-(d) immediately above optionally is substituted with one or more chemical moieties selected from the groups consisting of:

(i) a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; and a nitro group; and

(ii) a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; and a sulfonyl ester group;

wherein each of the moieties of (ii) immediately above optionally is substituted with one or more chemical moieties selected from the group consisting of: a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; a nitro group, a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; a sulfonyl ester group; and a 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms; and

(iii) a 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms;

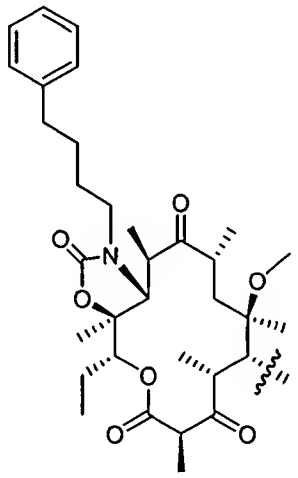
wherein the 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms optionally is substituted with one or more chemical moieties selected from the groups consisting of:

(1) a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; and a nitro group; and

(2) a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; and a sulfonyl ester group;

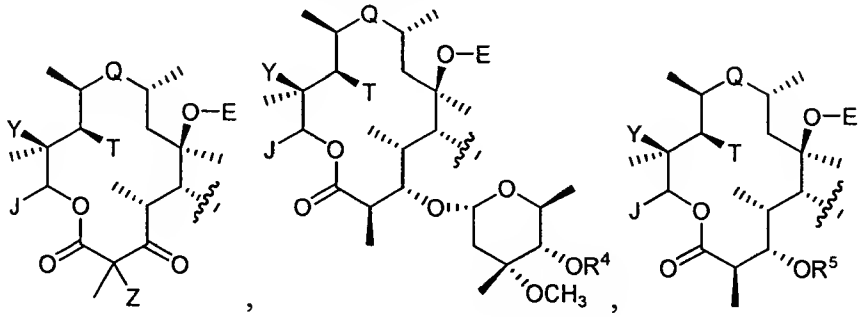
wherein each of the moieties of (iii)(2) immediately above optionally is substituted with one or more chemical moieties selected from the group consisting of: a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; a nitro group, a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; and a sulfonyl ester group;

provided that when M is



m is not 0 or 1.

In embodiments of the foregoing compounds, M is selected from the group consisting of:



and pharmaceutically acceptable salts, esters and prodrugs thereof, wherein

(a) E is selected from the group consisting of: hydrogen, a C_{1-6}-alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, –C(O)-R^6, –C(O)-C_{1-6} alkyl group-R^6, -C(O)-C_{2-6} alkenyl group-R^6, –C(O)-C_{2-6} alkynyl group-R^6, -C_{1-6} alkyl group-G-R^6, -C_{2-6} alkenyl group-G-R^6; and -C_{2-6} alkynyl group-G-R^6;

wherein

(i) the C_{1-6}-alkyl group, the C_{2-6} alkenyl group, and the C_{2-6} alkynyl group optionally are substituted with one or more substituents selected from the group consisting of: a halogen, an aryl group, a substituted aryl group, a heterocyclic group, a substituted heterocyclic group, -OR^6, -O-C_{1-6} alkyl group-R^6, -O-C_{2-6} alkenyl group-R^6, -O-C_{2-6} alkynyl group-R^6, and–NR^7R^8;

(ii) R^6 is selected from the group consisting of: hydrogen, an aryl group, a substituted aryl group, a heterocyclic group, and a substituted heterocyclic group;

(iii) R^7 and R^8 independently are selected from the group consisting of: hydrogen, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group,

wherein

the C_{1-6} alkyl group, the C_{2-6} alkenyl group, and the C_{2-6} alkynyl group are optionally substituted with one or more substituents selected from the group consisting of: halogen, an aryl group, a substituted aryl group, a heterocyclic group, a substituted heterocyclic group, –OR^5, and –NR^9R^{10};

wherein

R^9 and R^{10} independently are selected from the group consisting of: hydrogen, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group; or

R^9 and R^{10} taken together with the nitrogen atom to which they are connected form a 3- to 7-membered ring, optionally containing one or more substituents selected from the group consisting of: –O–, –NH–, -N(C_{1-6} alkyl group) –, -N(aryl)–, –N(heteroaryl)–, –S–, -S(O)–, –SO_2–, and –C(O)–; or

R^7 and R^8 taken together with the nitrogen atom to which they are connected form a 3- to 7-membered ring, optionally containing one or more substituents selected

from the group consisting of: –O–, –NH–, –N(C_{1-6} alkyl group) –, -N(aryl)–, -N(heteroaryl)–, -S–, -S(O)–, –SO_2–, and –C(O)–; and

(iv) G is selected from the group consisting of: –OC(O) –, -OC(O)O–, –OC(O)NR^7-, –C(O)NR^7–, –NR^7C(O)–, –NR^7C(O)O–, –NR^7C(O)NR^8–, -NR^7C(NH)NR^8–, -S-, –S(O)-, and –SO_2-;

(b) R^4 is selected from the group consisting of: hydrogen, a hydroxy protecting group, -C_{1-6} alkyl group–G–R^6, –C_{2-6} alkenyl–G–R^6, and –C_{2-6} alkynyl–G–R^6;

(c) R^5 is selected from the group consisting of: hydrogen, a hydroxy protecting group, R^6, -V-W-R^6, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group,

wherein

(i) V is -C(O)-, -C(O)O-, -C(O)NR^7-, or absent;

(ii) W is a C_{1-6} alkyl group, a C_{2-6} alkenyl group, C_{2-6} alkynyl group, or absent; and

(iii) the C_{1-6} alkyl group, the C_{2-6} alkenyl group, and the C_{2-6} alkynyl group are optionally substituted with one or more substituents selected from the group consisting of: a halogen, an aryl group, a substituted aryl group, a heteroaryl group, a substituted heteroaryl group, –OR^6, -O-C_{1-6} alkyl group-R^6, -O-C_{2-6} alkenyl group-R^6, -O-C_{2-6} alkynyl group-R^6, and -NR^7R^8;

(d) Q is selected from the group consisting of: –NR^7CH_2–, –CH_2-NR^7–, -C(O)–, -C(=NOR^6)–, –C(=N-NR^7R^8)–, -CH(-OR^6)–, and –CH(-NR^7R^8)–;

(e) J is selected from the group consisting of: –CH_3, –CH_2CH_3, –$CH(OH)CH_3$, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group;

wherein

the C_{1-6} alkyl group, the C_{2-6} alkenyl group; and the C_{2-6} alkynyl group optionally are substituted with one or more substituents selected from the group consisting of: an aryl group, a substituted aryl group, a heteroaryl group, and a substituted heteroaryl group;

(f) T is selected from the group consisting of: $-OR^5$, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, $-NR^7R^8$, $-C(O)-R^6$, $-C(O)-C_{1-6}$ alkyl group-R^6, $-C(O)-C_{2-6}$ alkenyl group-R^6, $-C(O)-C_{2-6}$ alkynyl group-R^6,

wherein

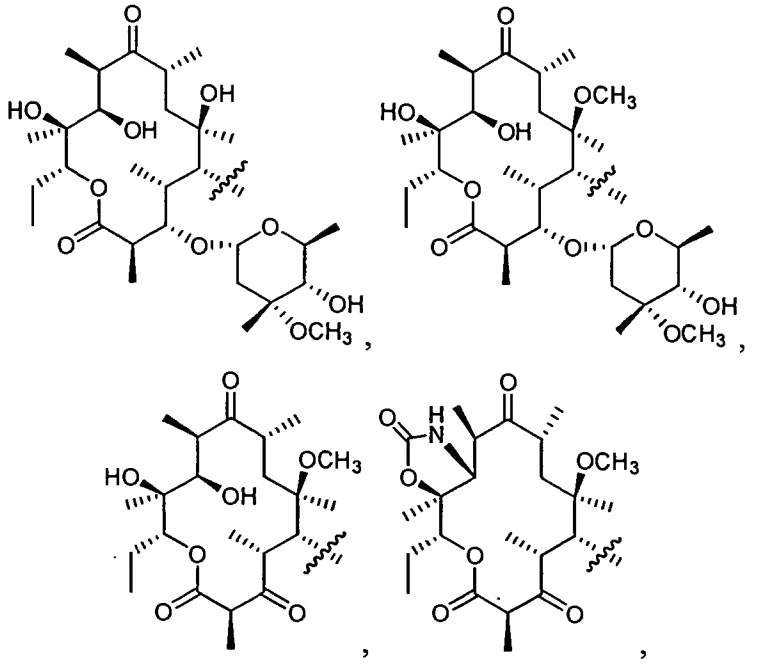
the C_{1-6} alkyl group, the C_{2-6} alkenyl group, and the C_{2-6} alkynyl group optionally are substituted with one or more substituents selected from the group consisting of: a halogen, an aryl group, a substituted aryl group, a heterocyclic group, a substituted heterocyclic group, $-OR^6$, $-O-C_{1-6}$ alkyl group-R^6, $-O-C_{2-6}$ alkenyl group-R^6, $-O-C_{2-6}$ alkynyl group-R^6, and $-NR^7R^8$; and

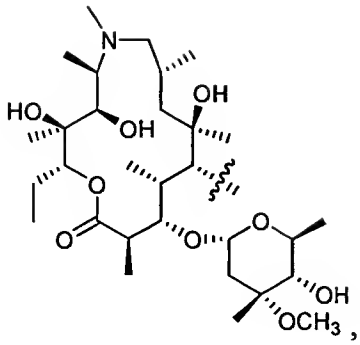
Y is $-OR^5$; or

T and Y taken together with the atoms to which they are attached form a 5-membered ring by attachment to each other through a linker selected from the group consisting of: $-OC(O)O-$, $-OC(O)NR^7-$, $-OC(S)O-$, $-OC(S)NR^7-$, $-OC(O)CHR^7-$, and $-OC(S)CHR^7$; and

(g) Z is selected from the group consisting of: hydrogen, methyl, and a halogen.

In preferred embodiments of the foregoing compounds, M is selected from the group consisting of:

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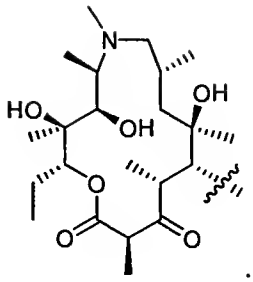
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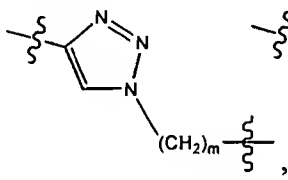
In preferred embodiments of the foregoing compounds, L-$(CH_2)_m$ is selected from the group consisting of: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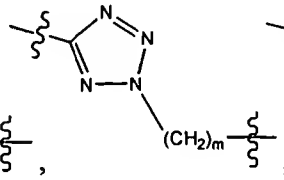
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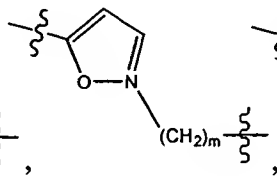
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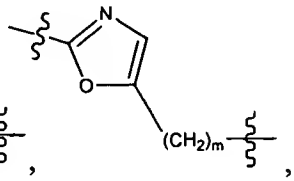
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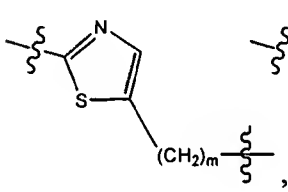
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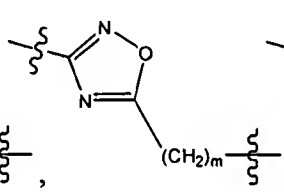
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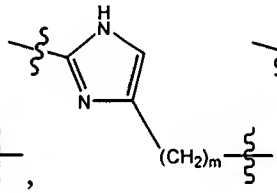
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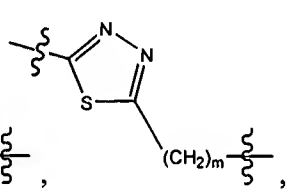
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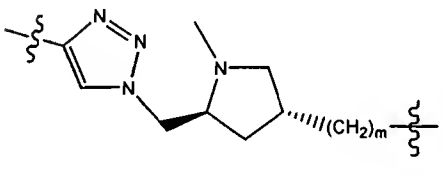
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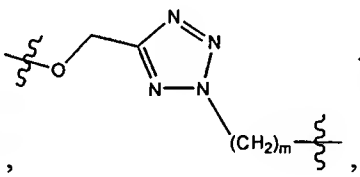
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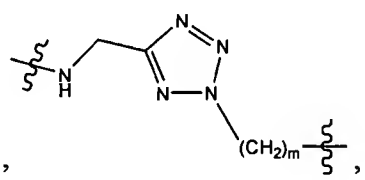
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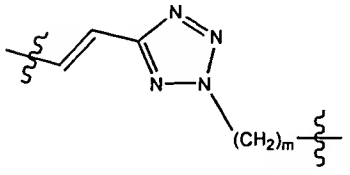
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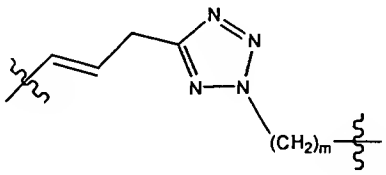
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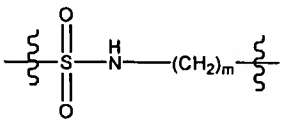
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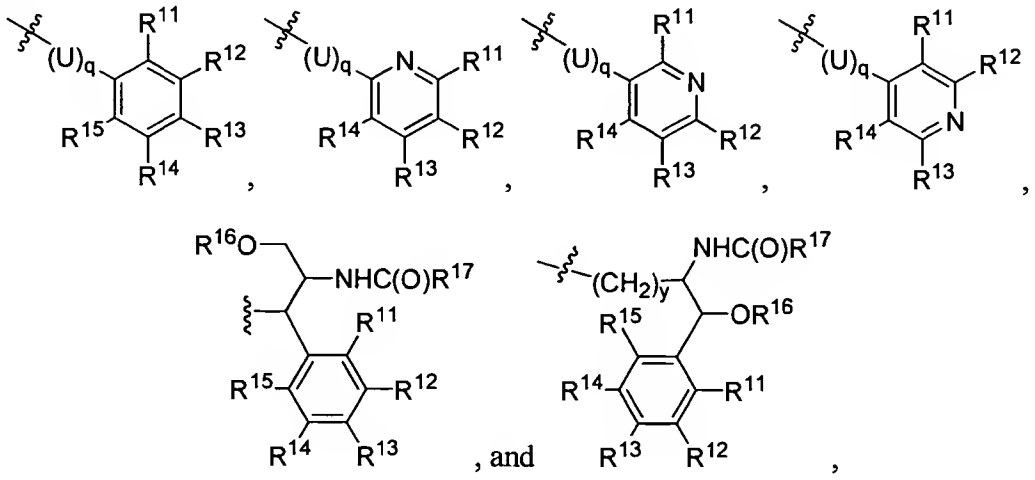
In preferred embodiments of the foregoing compounds, A is selected from the group consisting of:



wherein

R^{11}, R^{12}, R^{13}, R^{14}, and R^{15} independently are selected from the group consisting of: $-R^7$, $-OR^7$, $-NHC(O)R^7$, $-C(O)R^7$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-SO_2NR^7R^8$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NO_2$, -F, -Cl, -Br, -I, and a 5- or 6-membered saturated, unsaturated or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms,

wherein the 5- or 6-membered saturated, unsaturated or aromatic heterocyclic ring optionally is substituted with one or more chemical moieties selected from the group consisting of: $-R^7$, $-OR^7$, $-NHC(O)R^7$, $-C(O)R^7$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-SO_2NR^7R^8$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NO_2$, -F, -Cl, -Br, and -I;

R^{16} is hydrogen or a hydroxy protecting group;

R^{17} is methyl, a mono-halomethyl group, di-halomethyl group, or a tri-halomethyl group;

U is selected from the group consisting of: -O-, -NH-, $-NR^7$-, -S-, -S(O)-, $-SO_2$-, $-SO_2NH$-, $-SO_2NR^7$-, -C(O)-, -C(O)NH-, $-C(O)NR^7$-, -C(NOH)-, $-C(NOR^7)$-, and –C(S)-;

q is 0 or 1;

y is 0, 1, 2, or 3; and

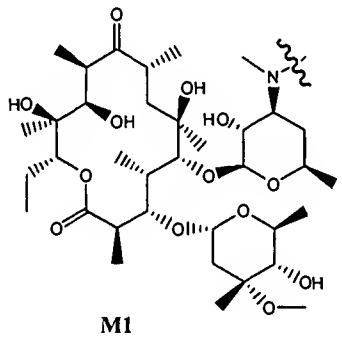
R^7 and R^8 are as defined above.

In other preferred embodiments of the foregoing compounds, U is –O- and q is 1. In yet other preferred embodiments of the foregoing compounds, n is 1, 2, 3, or 4, and m is 0, 1, or 2.

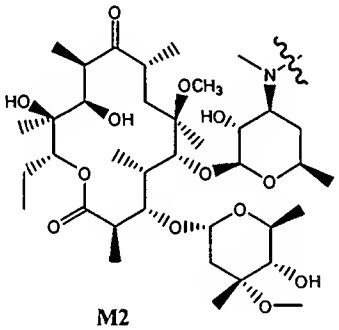
In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of one or more of the foregoing compounds and a pharmaceutically acceptable carrier. In yet another aspect, the invention provides a method for treating a microbial infection, a fungal infection, a parasitic disease, a proliferative disease, a viral infection, an inflammatory disease, or a gastrointestinal motility disorder in a mammal by administering effective amounts of the compounds of the invention or pharmaceutical compositions of the invention. In still another aspect, the invention provides methods for synthesizing any one of the foregoing compounds.

In preferred embodiments, the invention relates to a family of compounds comprising an aromatic or heteroaromatic ring linked via a linker to at least a portion of a macrolide-based antibiotic. Exemplary macrolides, linkers, and aromatic groups useful in the synthesis of the compounds of the invention include, but are not limited to, the chemical structures shown below.

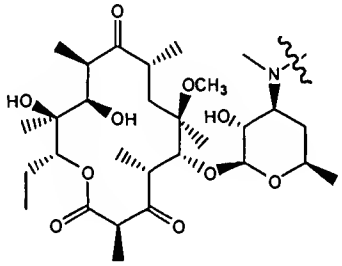
Macrolides



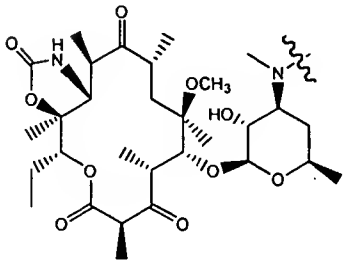
M1



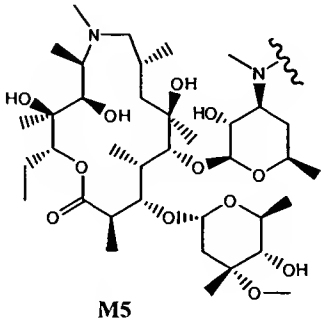
M2



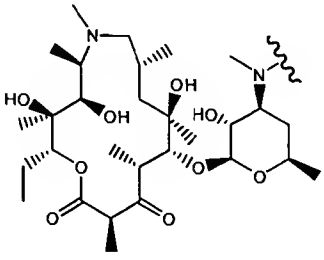
M3



M4

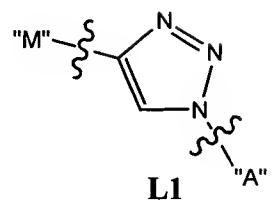


M5

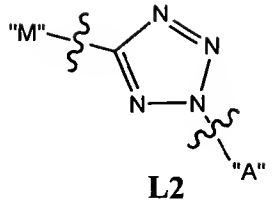


M6

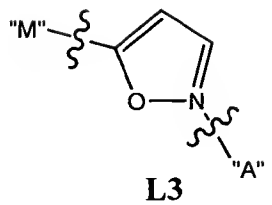
Linkers



L1



L2



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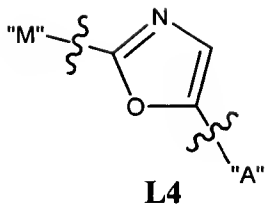

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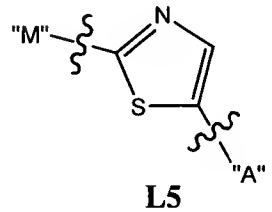

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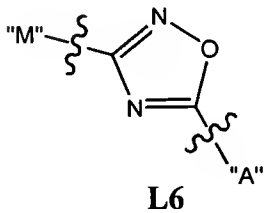

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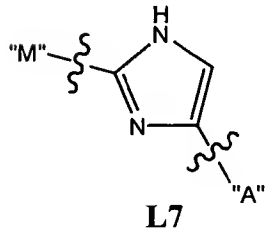

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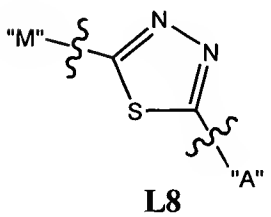

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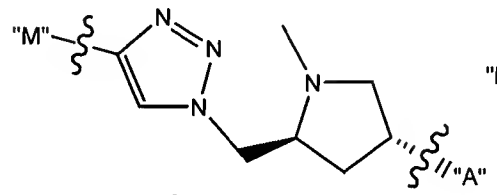

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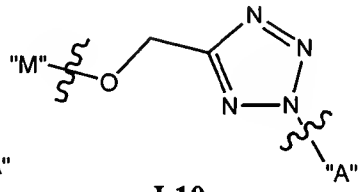

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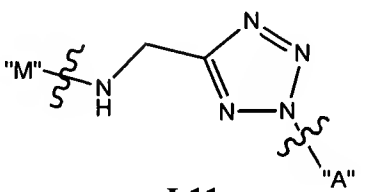

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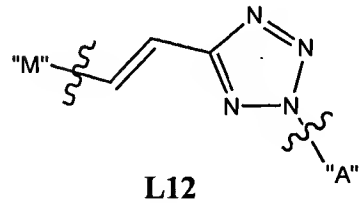

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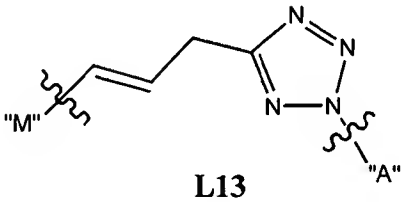
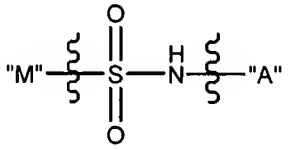


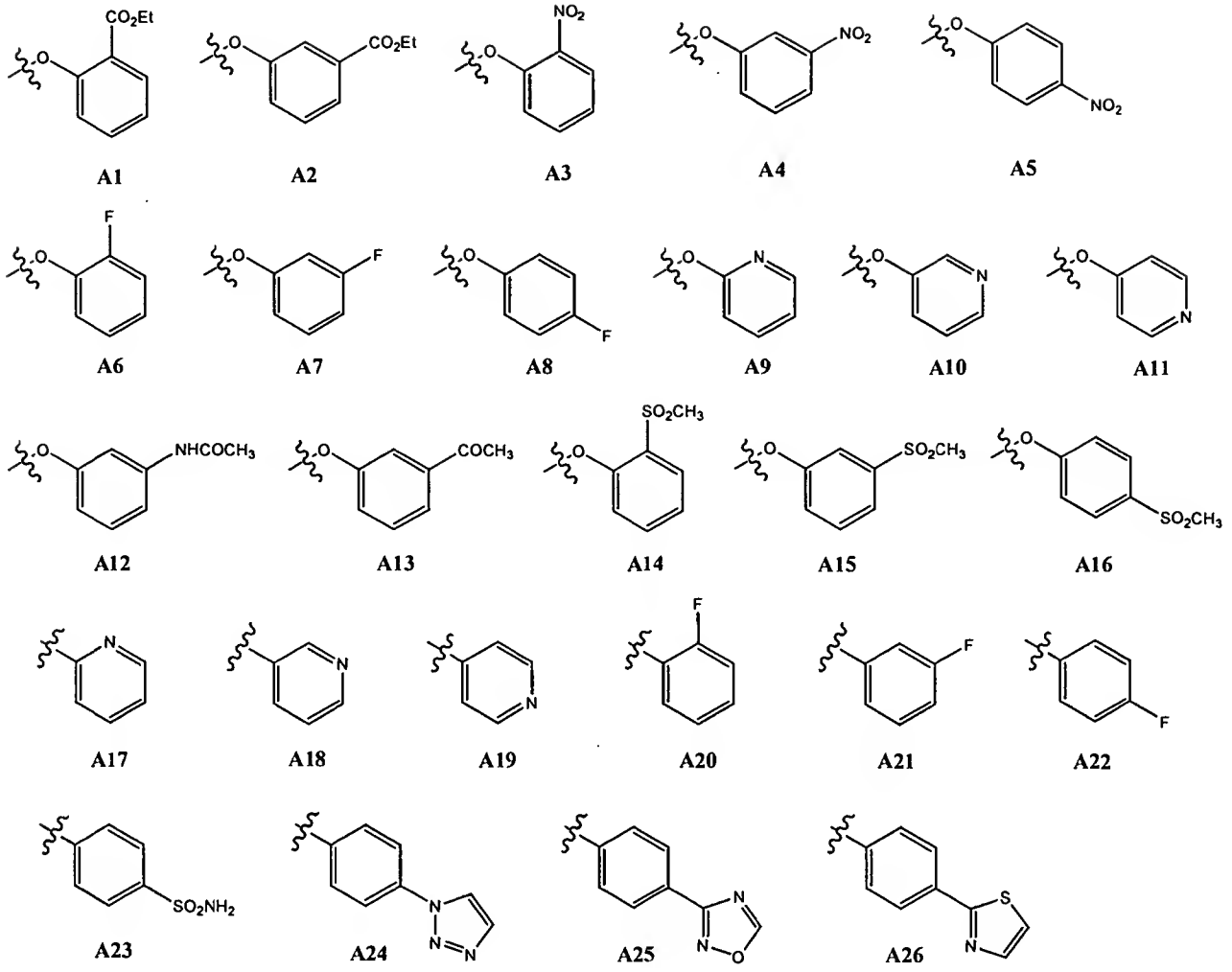
L13



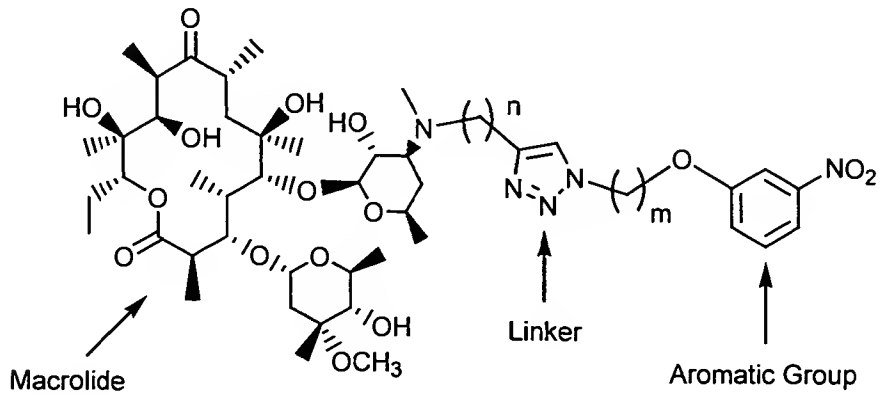
L14

For the above linker groups, it should be understood that "M" and "A" are included to depict the orientation of the linker group with respect to the other structures that define the compounds of the invention. More specifically, "M" denotes the portion of the compound that includes the macrolide and "A" denotes the portion of the compound that includes the aromatic group.

Aromatic Groups



An exemplary scheme showing the linkage of a macrolide to an aromatic group via a triazole linker, optionally including straight chain alkyl groups on either or both sides, is shown below, where each of n and m independently are 0 to 6.



The various macrolides can be linked via the linkers to the aromatic groups using conventional chemistries known in the art, such as those described below. Using the various combinations of macrolides, linkers, and aromatic groups, the skilled artisan can synthesize the exemplary compounds listed in Table 2. For each set of examples, the 49 lower case letter designations, i.e. "**a**" through "**w'**," denote the 49 compounds defined where n and m vary independently between 0 1, 2, 3, 4, 5, or 6. For example, as a guide to the following table, compound **E1a** is the n = 0, m = 0 variant of the structure shown on the same row of the table. Similarly, compound **E1b** is the n = 1, m = 0 derivative, and compound **E1c** is the n = 2, m = 0 derivative, etc. For convenience, Table 1 lists the 49 letter designations and their corresponding n and m values.

TABLE 1

	n	m
a	0	0
b	1	0
c	2	0
d	3	0
e	4	0
f	5	0
g	6	0
h	0	1
i	1	1
j	2	1
k	3	1
l	4	1
m	5	1
n	6	1
o	0	2
p	1	2
q	2	2
r	3	2
s	4	2
t	5	2
u	6	2
v	0	3
w	1	3
x	2	3
y	3	3
z	4	3
a'	5	3

b'	6	3
c'	0	4
d'	1	4
e'	2	4
f'	3	4
g'	4	4
h'	5	4
i'	6	4
j'	0	5
k'	1	5
l'	2	5
m'	3	5
n'	4	5
o'	5	5
p'	6	5
q'	0	6
r'	1	6
s'	2	6
t'	3	6
u'	4	6
v'	5	6
w'	6	6

TABLE 2

Example	M Group	L Group	A Group
E1a-w'	M1	L1	A1
E2a-w'	M1	L1	A2
E3a-w'	M1	L1	A3
E4a-w'	M1	L1	A4
E5a-w'	M1	L1	A5
E6a-w'	M1	L1	A6
E7a-w'	M1	L1	A7
E8a-w'	M1	L1	A8
E9a-w'	M1	L1	A9
E10a-w'	M1	L1	A10
E11a-w'	M1	L1	A11
E12a-w'	M1	L1	A12
E13a-w'	M1	L1	A13
E14a-w'	M1	L1	A14
E15a-w'	M1	L1	A15
E16a-w'	M1	L1	A16
E17a-w'	M1	L1	A17
E18a-w'	M1	L1	A18
E19a-w'	M1	L1	A19

E20a-w'	M1	L1	A20
E21a-w'	M1	L1	A21
E22a-w'	M1	L1	A22
E23a-w'	M1	L1	A23
E24a-w'	M1	L1	A24
E25a-w'	M1	L1	A25
E26a-w'	M1	L1	A26
E27a-w'	M1	L2	A1
E28a-w'	M1	L2	A2
E29a-w'	M1	L2	A3
E30a-w'	M1	L2	A4
E31a-w'	M1	L2	A5
E32a-w'	M1	L2	A6
E33a-w'	M1	L2	A7
E34a-w'	M1	L2	A8
E35a-w'	M1	L2	A9
E36a-w'	M1	L2	A10
E37a-w'	M1	L2	A11
E38a-w'	M1	L2	A12
E39a-w'	M1	L2	A13
E40a-w'	M1	L2	A14
E41a-w'	M1	L2	A15
E42a-w'	M1	L2	A16
E43a-w'	M1	L2	A17
E44a-w'	M1	L2	A18
E45a-w'	M1	L2	A19
E46a-w'	M1	L2	A20
E47a-w'	M1	L2	A21
E48a-w'	M1	L2	A22
E49a-w'	M1	L2	A23
E50a-w'	M1	L2	A24
E51a-w'	M1	L2	A25
E52a-w'	M1	L2	A26
E53a-w'	M1	L3	A1
E54a-w'	M1	L3	A2
E55a-w'	M1	L3	A3
E56a-w'	M1	L3	A4
E57a-w'	M1	L3	A5
E58a-w'	M1	L3	A6
E59a-w'	M1	L3	A7
E60a-w'	M1	L3	A8
E61a-w'	M1	L3	A9
E62a-w'	M1	L3	A10
E63a-w'	M1	L3	A11
E64a-w'	M1	L3	A12

E65a-w'	M1	L3	A13
E66a-w'	M1	L3	A14
E67a-w'	M1	L3	A15
E68a-w'	M1	L3	A16
E69a-w'	M1	L3	A17
E70a-w'	M1	L3	A18
E71a-w'	M1	L3	A19
E72a-w'	M1	L3	A20
E73a-w'	M1	L3	A21
E74a-w'	M1	L3	A22
E75a-w'	M1	L3	A23
E76a-w'	M1	L3	A24
E77a-w'	M1	L3	A25
E78a-w'	M1	L3	A26
E79a-w'	M1	L4	A1
E80a-w'	M1	L4	A2
E81a-w'	M1	L4	A3
E82a-w'	M1	L4	A4
E83a-w'	M1	L4	A5
E84a-w'	M1	L4	A6
E85a-w'	M1	L4	A7
E86a-w'	M1	L4	A8
E87a-w'	M1	L4	A9
E88a-w'	M1	L4	A10
E89a-w'	M1	L4	A11
E90a-w'	M1	L4	A12
E91a-w'	M1	L4	A13
E92a-w'	M1	L4	A14
E93a-w'	M1	L4	A15
E94a-w'	M1	L4	A16
E95a-w'	M1	L4	A17
E96a-w'	M1	L4	A18
E97a-w'	M1	L4	A19
E98a-w'	M1	L4	A20
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E100a-w'	M1	L4	A22
E101a-w'	M1	L4	A23
E102a-w'	M1	L4	A24
E103a-w'	M1	L4	A25
E104a-w'	M1	L4	A26
E105a-w'	M1	L5	A1
E106a-w'	M1	L5	A2
E107a-w'	M1	L5	A3
E108a-w'	M1	L5	A4
E109a-w'	M1	L5	A5

E110a-w'	M1	L5	A6
E111a-w'	M1	L5	A7
E112a-w'	M1	L5	A8
E113a-w'	M1	L5	A9
E114a-w'	M1	L5	A10
E115a-w'	M1	L5	A11
E116a-w'	M1	L5	A12
E117a-w'	M1	L5	A13
E118a-w'	M1	L5	A14
E119a-w'	M1	L5	A15
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E121a-w'	M1	L5	A17
E122a-w'	M1	L5	A18
E123a-w'	M1	L5	A19
E124a-w'	M1	L5	A20
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E127a-w'	M1	L5	A23
E128a-w'	M1	L5	A24
E129a-w'	M1	L5	A25
E130a-w'	M1	L5	A26
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E132a-w'	M1	L6	A2
E133a-w'	M1	L6	A3
E134a-w'	M1	L6	A4
E135a-w'	M1	L6	A5
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E288a-w'	M1	L12	A2
E289a-w'	M1	L12	A3

E290a-w'	M1	L12	A4
E291a-w'	M1	L12	A5
E292a-w'	M1	L12	A6
E293a-w'	M1	L12	A7
E294a-w'	M1	L12	A8
E295a-w'	M1	L12	A9
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E300a-w'	M1	L12	A14
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E312a-w'	M1	L12	A26
E313a-w'	M1	L13	A1
E314a-w'	M1	L13	A2
E315a-w'	M1	L13	A3
E316a-w'	M1	L13	A4
E317a-w'	M1	L13	A5
E318a-w'	M1	L13	A6
E319a-w'	M1	L13	A7
E320a-w'	M1	L13	A8
E321a-w'	M1	L13	A9
E322a-w'	M1	L13	A10
E323a-w'	M1	L13	A11
E324a-w'	M1	L13	A12
E325a-w'	M1	L13	A13
E326a-w'	M1	L13	A14
E327a-w'	M1	L13	A15
E328a-w'	M1	L13	A16
E329a-w'	M1	L13	A17
E330a-w'	M1	L13	A18
E331a-w'	M1	L13	A19
E332a-w'	M1	L13	A20
E333a-w'	M1	L13	A21
E334a-w'	M1	L13	A22

E335a-w'	M1	L13	A23
E336a-w'	M1	L13	A24
E337a-w'	M1	L13	A25
E338a-w'	M1	L13	A26
E339a-w'	M1	L14	A1
E340a-w'	M1	L14	A2
E341a-w'	M1	L14	A3
E342a-w'	M1	L14	A4
E343a-w'	M1	L14	A5
E344a-w'	M1	L14	A6
E345a-w'	M1	L14	A7
E346a-w'	M1	L14	A8
E347a-w'	M1	L14	A9
E348a-w'	M1	L14	A10
E349a-w'	M1	L14	A11
E350a-w'	M1	L14	A12
E351a-w'	M1	L14	A13
E352a-w'	M1	L14	A14
E353a-w'	M1	L14	A15
E354a-w'	M1	L14	A16
E355a-w'	M1	L14	A17
E356a-w'	M1	L14	A18
E357a-w'	M1	L14	A19
E358a-w'	M1	L14	A20
E359a-w'	M1	L14	A21
E360a-w'	M1	L14	A22
E361a-w'	M1	L14	A23
E362a-w'	M1	L14	A24
E363a-w'	M1	L14	A25
E364a-w'	M1	L14	A26
E365a-w'	M2	L1	A1
E366a-w'	M2	L1	A2
E367a-w'	M2	L1	A3
E368a-w'	M2	L1	A4
E369a-w'	M2	L1	A5
E370a-w'	M2	L1	A6
E371a-w'	M2	L1	A7
E372a-w'	M2	L1	A8
E373a-w'	M2	L1	A9
E374a-w'	M2	L1	A10
E375a-w'	M2	L1	A11
E376a-w'	M2	L1	A12
E377a-w'	M2	L1	A13
E378a-w'	M2	L1	A14
E379a-w'	M2	L1	A15

E380a-w'	M2	L1	A16
E381a-w'	M2	L1	A17
E382a-w'	M2	L1	A18
E383a-w'	M2	L1	A19
E384a-w'	M2	L1	A20
E385a-w'	M2	L1	A21
E386a-w'	M2	L1	A22
E387a-w'	M2	L1	A23
E388a-w'	M2	L1	A24
E389a-w'	M2	L1	A25
E390a-w'	M2	L1	A26
E391a-w'	M2	L2	A1
E392a-w'	M2	L2	A2
E393a-w'	M2	L2	A3
E394a-w'	M2	L2	A4
E395a-w'	M2	L2	A5
E396a-w'	M2	L2	A6
E397a-w'	M2	L2	A7
E398a-w'	M2	L2	A8
E399a-w'	M2	L2	A9
E400a-w'	M2	L2	A10
E401a-w'	M2	L2	A11
E402a-w'	M2	L2	A12
E403a-w'	M2	L2	A13
E404a-w'	M2	L2	A14
E405a-w'	M2	L2	A15
E406a-w'	M2	L2	A16
E407a-w'	M2	L2	A17
E408a-w'	M2	L2	A18
E409a-w'	M2	L2	A19
E410a-w'	M2	L2	A20
E411a-w'	M2	L2	A21
E412a-w'	M2	L2	A22
E413a-w'	M2	L2	A23
E414a-w'	M2	L2	A24
E415a-w'	M2	L2	A25
E416a-w'	M2	L2	A26
E417a-w'	M2	L3	A1
E418a-w'	M2	L3	A2
E419a-w'	M2	L3	A3
E420a-w'	M2	L3	A4
E421a-w'	M2	L3	A5
E422a-w'	M2	L3	A6
E423a-w'	M2	L3	A7
E424a-w'	M2	L3	A8

E425a-w'	M2	L3	A9
E426a-w'	M2	L3	A10
E427a-w'	M2	L3	A11
E428a-w'	M2	L3	A12
E429a-w'	M2	L3	A13
E430a-w'	M2	L3	A14
E431a-w'	M2	L3	A15
E432a-w'	M2	L3	A16
E433a-w'	M2	L3	A17
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E435a-w'	M2	L3	A19
E436a-w'	M2	L3	A20
E437a-w'	M2	L3	A21
E438a-w'	M2	L3	A22
E439a-w'	M2	L3	A23
E440a-w'	M2	L3	A24
E441a-w'	M2	L3	A25
E442a-w'	M2	L3	A26
E443a-w'	M2	L4	A1
E444a-w'	M2	L4	A2
E445a-w'	M2	L4	A3
E446a-w'	M2	L4	A4
E447a-w'	M2	L4	A5
E448a-w'	M2	L4	A6
E449a-w'	M2	L4	A7
E450a-w'	M2	L4	A8
E451a-w'	M2	L4	A9
E452a-w'	M2	L4	A10
E453a-w'	M2	L4	A11
E454a-w'	M2	L4	A12
E455a-w'	M2	L4	A13
E456a-w'	M2	L4	A14
E457a-w'	M2	L4	A15
E458a-w'	M2	L4	A16
E459a-w'	M2	L4	A17
E460a-w'	M2	L4	A18
E461a-w'	M2	L4	A19
E462a-w'	M2	L4	A20
E463a-w'	M2	L4	A21
E464a-w'	M2	L4	A22
E465a-w'	M2	L4	A23
E466a-w'	M2	L4	A24
E467a-w'	M2	L4	A25
E468a-w'	M2	L4	A26
E469a-w'	M2	L5	A1

E470a-w'	M2	L5	A2
E471a-w'	M2	L5	A3
E472a-w'	M2	L5	A4
E473a-w'	M2	L5	A5
E474a-w'	M2	L5	A6
E475a-w'	M2	L5	A7
E476a-w'	M2	L5	A8
E477a-w'	M2	L5	A9
E478a-w'	M2	L5	A10
E479a-w'	M2	L5	A11
E480a-w'	M2	L5	A12
E481a-w'	M2	L5	A13
E482a-w'	M2	L5	A14
E483a-w'	M2	L5	A15
E484a-w'	M2	L5	A16
E485a-w'	M2	L5	A17
E486a-w'	M2	L5	A18
E487a-w'	M2	L5	A19
E488a-w'	M2	L5	A20
E489a-w'	M2	L5	A21
E490a-w'	M2	L5	A22
E491a-w'	M2	L5	A23
E492a-w'	M2	L5	A24
E493a-w'	M2	L5	A25
E494a-w'	M2	L5	A26
E495a-w'	M2	L6	A1
E496a-w'	M2	L6	A2
E497a-w'	M2	L6	A3
E498a-w'	M2	L6	A4
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E500a-w'	M2	L6	A6
E501a-w'	M2	L6	A7
E502a-w'	M2	L6	A8
E503a-w'	M2	L6	A9
E504a-w'	M2	L6	A10
E505a-w'	M2	L6	A11
E506a-w'	M2	L6	A12
E507a-w'	M2	L6	A13
E508a-w'	M2	L6	A14
E509a-w'	M2	L6	A15
E510a-w'	M2	L6	A16
E511a-w'	M2	L6	A17
E512a-w'	M2	L6	A18
E513a-w'	M2	L6	A19
E514a-w'	M2	L6	A20

E515a-w'	M2	L6	A21
E516a-w'	M2	L6	A22
E517a-w'	M2	L6	A23
E518a-w'	M2	L6	A24
E519a-w'	M2	L6	A25
E520a-w'	M2	L6	A26
E521a-w'	M2	L7	A1
E522a-w'	M2	L7	A2
E523a-w'	M2	L7	A3
E524a-w'	M2	L7	A4
E525a-w'	M2	L7	A5
E526a-w'	M2	L7	A6
E527a-w'	M2	L7	A7
E528a-w'	M2	L7	A8
E529a-w'	M2	L7	A9
E530a-w'	M2	L7	A10
E531a-w'	M2	L7	A11
E532a-w'	M2	L7	A12
E533a-w'	M2	L7	A13
E534a-w'	M2	L7	A14
E535a-w'	M2	L7	A15
E536a-w'	M2	L7	A16
E537a-w'	M2	L7	A17
E538a-w'	M2	L7	A18
E539a-w'	M2	L7	A19
E540a-w'	M2	L7	A20
E541a-w'	M2	L7	A21
E542a-w'	M2	L7	A22
E543a-w'	M2	L7	A23
E544a-w'	M2	L7	A24
E545a-w'	M2	L7	A25
E546a-w'	M2	L7	A26
E547a-w'	M2	L8	A1
E548a-w'	M2	L8	A2
E549a-w'	M2	L8	A3
E550a-w'	M2	L8	A4
E551a-w'	M2	L8	A5
E552a-w'	M2	L8	A6
E553a-w'	M2	L8	A7
E554a-w'	M2	L8	A8
E555a-w'	M2	L8	A9
E556a-w'	M2	L8	A10
E557a-w'	M2	L8	A11
E558a-w'	M2	L8	A12
E559a-w'	M2	L8	A13

E560a-w'	M2	L8	A14
E561a-w'	M2	L8	A15
E562a-w'	M2	L8	A16
E563a-w'	M2	L8	A17
E564a-w'	M2	L8	A18
E565a-w'	M2	L8	A19
E566a-w'	M2	L8	A20
E567a-w'	M2	L8	A21
E568a-w'	M2	L8	A22
E569a-w'	M2	L8	A23
E570a-w'	M2	L8	A24
E571a-w'	M2	L8	A25
E572a-w'	M2	L8	A26
E573a-w'	M2	L9	A1
E574a-w'	M2	L9	A2
E575a-w'	M2	L9	A3
E576a-w'	M2	L9	A4
E577a-w'	M2	L9	A5
E578a-w'	M2	L9	A6
E579a-w'	M2	L9	A7
E580a-w'	M2	L9	A8
E581a-w'	M2	L9	A9
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E583a-w'	M2	L9	A11
E584a-w'	M2	L9	A12
E585a-w'	M2	L9	A13
E586a-w'	M2	L9	A14
E587a-w'	M2	L9	A15
E588a-w'	M2	L9	A16
E589a-w'	M2	L9	A17
E590a-w'	M2	L9	A18
E591a-w'	M2	L9	A19
E592a-w'	M2	L9	A20
E593a-w'	M2	L9	A21
E594a-w'	M2	L9	A22
E595a-w'	M2	L9	A23
E596a-w'	M2	L9	A24
E597a-w'	M2	L9	A25
E598a-w'	M2	L9	A26
E599a-w'	M2	L10	A1
E600a-w'	M2	L10	A2
E601a-w'	M2	L10	A3
E602a-w'	M2	L10	A4
E603a-w'	M2	L10	A5
E604a-w'	M2	L10	A6

E605a-w'	M2	L10	A7
E606a-w'	M2	L10	A8
E607a-w'	M2	L10	A9
E608a-w'	M2	L10	A10
E609a-w'	M2	L10	A11
E610a-w'	M2	L10	A12
E611a-w'	M2	L10	A13
E612a-w'	M2	L10	A14
E613a-w'	M2	L10	A15
E614a-w'	M2	L10	A16
E615a-w'	M2	L10	A17
E616a-w'	M2	L10	A18
E617a-w'	M2	L10	A19
E618a-w'	M2	L10	A20
E619a-w'	M2	L10	A21
E620a-w'	M2	L10	A22
E621a-w'	M2	L10	A23
E622a-w'	M2	L10	A24
E623a-w'	M2	L10	A25
E624a-w'	M2	L10	A26
E625a-w'	M2	L11	A1
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E627a-w'	M2	L11	A3
E628a-w'	M2	L11	A4
E629a-w'	M2	L11	A5
E630a-w'	M2	L11	A6
E631a-w'	M2	L11	A7
E632a-w'	M2	L11	A8
E633a-w'	M2	L11	A9
E634a-w'	M2	L11	A10
E635a-w'	M2	L11	A11
E636a-w'	M2	L11	A12
E637a-w'	M2	L11	A13
E638a-w'	M2	L11	A14
E639a-w'	M2	L11	A15
E640a-w'	M2	L11	A16
E641a-w'	M2	L11	A17
E642a-w'	M2	L11	A18
E643a-w'	M2	L11	A19
E644a-w'	M2	L11	A20
E645a-w'	M2	L11	A21
E646a-w'	M2	L11	A22
E647a-w'	M2	L11	A23
E648a-w'	M2	L11	A24
E649a-w'	M2	L11	A25

E650a-w'	M2	L11	A26
E651a-w'	M2	L12	A1
E652a-w'	M2	L12	A2
E653a-w'	M2	L12	A3
E654a-w'	M2	L12	A4
E655a-w'	M2	L12	A5
E656a-w'	M2	L12	A6
E657a-w'	M2	L12	A7
E658a-w'	M2	L12	A8
E659a-w'	M2	L12	A9
E660a-w'	M2	L12	A10
E661a-w'	M2	L12	A11
E662a-w'	M2	L12	A12
E663a-w'	M2	L12	A13
E664a-w'	M2	L12	A14
E665a-w'	M2	L12	A15
E666a-w'	M2	L12	A16
E667a-w'	M2	L12	A17
E668a-w'	M2	L12	A18
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E671a-w'	M2	L12	A21
E672a-w'	M2	L12	A22
E673a-w'	M2	L12	A23
E674a-w'	M2	L12	A24
E675a-w'	M2	L12	A25
E676a-w'	M2	L12	A26
E677a-w'	M2	L13	A1
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E679a-w'	M2	L13	A3
E680a-w'	M2	L13	A4
E681a-w'	M2	L13	A5
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E683a-w'	M2	L13	A7
E684a-w'	M2	L13	A8
E685a-w'	M2	L13	A9
E686a-w'	M2	L13	A10
E687a-w'	M2	L13	A11
E688a-w'	M2	L13	A12
E689a-w'	M2	L13	A13
E690a-w'	M2	L13	A14
E691a-w'	M2	L13	A15
E692a-w'	M2	L13	A16
E693a-w'	M2	L13	A17
E694a-w'	M2	L13	A18

E695a-w'	M2	L13	A19
E696a-w'	M2	L13	A20
E697a-w'	M2	L13	A21
E698a-w'	M2	L13	A22
E699a-w'	M2	L13	A23
E700a-w'	M2	L13	A24
E701a-w'	M2	L13	A25
E702a-w'	M2	L13	A26
E703a-w'	M2	L14	A1
E704a-w'	M2	L14	A2
E705a-w'	M2	L14	A3
E706a-w'	M2	L14	A4
E707a-w'	M2	L14	A5
E708a-w'	M2	L14	A6
E709a-w'	M2	L14	A7
E710a-w'	M2	L14	A8
E711a-w'	M2	L14	A9
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E713a-w'	M2	L14	A11
E714a-w'	M2	L14	A12
E715a-w'	M2	L14	A13
E716a-w'	M2	L14	A14
E717a-w'	M2	L14	A15
E718a-w'	M2	L14	A16
E719a-w'	M2	L14	A17
E720a-w'	M2	L14	A18
E721a-w'	M2	L14	A19
E722a-w'	M2	L14	A20
E723a-w'	M2	L14	A21
E724a-w'	M2	L14	A22
E725a-w'	M2	L14	A23
E726a-w'	M2	L14	A24
E727a-w'	M2	L14	A25
E728a-w'	M2	L14	A26
E729a-w'	M3	L1	A1
E730a-w'	M3	L1	A2
E731a-w'	M3	L1	A3
E732a-w'	M3	L1	A4
E733a-w'	M3	L1	A5
E734a-w'	M3	L1	A6
E735a-w'	M3	L1	A7
E736a-w'	M3	L1	A8
E737a-w'	M3	L1	A9
E738a-w'	M3	L1	A10
E739a-w'	M3	L1	A11

E740a-w'	M3	L1	A12
E741a-w'	M3	L1	A13
E742a-w'	M3	L1	A14
E743a-w'	M3	L1	A15
E744a-w'	M3	L1	A16
E745a-w'	M3	L1	A17
E746a-w'	M3	L1	A18
E747a-w'	M3	L1	A19
E748a-w'	M3	L1	A20
E749a-w'	M3	L1	A21
E750a-w'	M3	L1	A22
E751a-w'	M3	L1	A23
E752a-w'	M3	L1	A24
E753a-w'	M3	L1	A25
E754a-w'	M3	L1	A26
E755a-w'	M3	L2	A1
E756a-w'	M3	L2	A2
E757a-w'	M3	L2	A3
E758a-w'	M3	L2	A4
E759a-w'	M3	L2	A5
E760a-w'	M3	L2	A6
E761a-w'	M3	L2	A7
E762a-w'	M3	L2	A8
E763a-w'	M3	L2	A9
E764a-w'	M3	L2	A10
E765a-w'	M3	L2	A11
E766a-w'	M3	L2	A12
E767a-w'	M3	L2	A13
E768a-w'	M3	L2	A14
E769a-w'	M3	L2	A15
E770a-w'	M3	L2	A16
E771a-w'	M3	L2	A17
E772a-w'	M3	L2	A18
E773a-w'	M3	L2	A19
E774a-w'	M3	L2	A20
E775a-w'	M3	L2	A21
E776a-w'	M3	L2	A22
E777a-w'	M3	L2	A23
E778a-w'	M3	L2	A24
E779a-w'	M3	L2	A25
E780a-w'	M3	L2	A26
E781a-w'	M3	L3	A1
E782a-w'	M3	L3	A2
E783a-w'	M3	L3	A3
E784a-w'	M3	L3	A4

E785a-w'	M3	L3	A5
E786a-w'	M3	L3	A6
E787a-w'	M3	L3	A7
E788a-w'	M3	L3	A8
E789a-w'	M3	L3	A9
E790a-w'	M3	L3	A10
E791a-w'	M3	L3	A11
E792a-w'	M3	L3	A12
E793a-w'	M3	L3	A13
E794a-w'	M3	L3	A14
E795a-w'	M3	L3	A15
E796a-w'	M3	L3	A16
E797a-w'	M3	L3	A17
E798a-w'	M3	L3	A18
E799a-w'	M3	L3	A19
E800a-w'	M3	L3	A20
E801a-w'	M3	L3	A21
E802a-w'	M3	L3	A22
E803a-w'	M3	L3	A23
E804a-w'	M3	L3	A24
E805a-w'	M3	L3	A25
E806a-w'	M3	L3	A26
E807a-w'	M3	L4	A1
E808a-w'	M3	L4	A2
E809a-w'	M3	L4	A3
E810a-w'	M3	L4	A4
E811a-w'	M3	L4	A5
E812a-w'	M3	L4	A6
E813a-w'	M3	L4	A7
E814a-w'	M3	L4	A8
E815a-w'	M3	L4	A9
E816a-w'	M3	L4	A10
E817a-w'	M3	L4	A11
E818a-w'	M3	L4	A12
E819a-w'	M3	L4	A13
E820a-w'	M3	L4	A14
E821a-w'	M3	L4	A15
E822a-w'	M3	L4	A16
E823a-w'	M3	L4	A17
E824a-w'	M3	L4	A18
E825a-w'	M3	L4	A19
E826a-w'	M3	L4	A20
E827a-w'	M3	L4	A21
E828a-w'	M3	L4	A22
E829a-w'	M3	L4	A23

E830a-w'	M3	L4	A24
E831a-w'	M3	L4	A25
E832a-w'	M3	L4	A26
E833a-w'	M3	L5	A1
E834a-w'	M3	L5	A2
E835a-w'	M3	L5	A3
E836a-w'	M3	L5	A4
E837a-w'	M3	L5	A5
E838a-w'	M3	L5	A6
E839a-w'	M3	L5	A7
E840a-w'	M3	L5	A8
E841a-w'	M3	L5	A9
E842a-w'	M3	L5	A10
E843a-w'	M3	L5	A11
E844a-w'	M3	L5	A12
E845a-w'	M3	L5	A13
E846a-w'	M3	L5	A14
E847a-w'	M3	L5	A15
E848a-w'	M3	L5	A16
E849a-w'	M3	L5	A17
E850a-w'	M3	L5	A18
E851a-w'	M3	L5	A19
E852a-w'	M3	L5	A20
E853a-w'	M3	L5	A21
E854a-w'	M3	L5	A22
E855a-w'	M3	L5	A23
E856a-w'	M3	L5	A24
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E858a-w'	M3	L5	A26
E859a-w'	M3	L6	A1
E860a-w'	M3	L6	A2
E861a-w'	M3	L6	A3
E862a-w'	M3	L6	A4
E863a-w'	M3	L6	A5
E864a-w'	M3	L6	A6
E865a-w'	M3	L6	A7
E866a-w'	M3	L6	A8
E867a-w'	M3	L6	A9
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E871a-w'	M3	L6	A13
E872a-w'	M3	L6	A14
E873a-w'	M3	L6	A15
E874a-w'	M3	L6	A16

E875a-w'	M3	L6	A17
E876a-w'	M3	L6	A18
E877a-w'	M3	L6	A19
E878a-w'	M3	L6	A20
E879a-w'	M3	L6	A21
E880a-w'	M3	L6	A22
E881a-w'	M3	L6	A23
E882a-w'	M3	L6	A24
E883a-w'	M3	L6	A25
E884a-w'	M3	L6	A26
E885a-w'	M3	L7	A1
E886a-w'	M3	L7	A2
E887a-w'	M3	L7	A3
E888a-w'	M3	L7	A4
E889a-w'	M3	L7	A5
E890a-w'	M3	L7	A6
E891a-w'	M3	L7	A7
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E895a-w'	M3	L7	A11
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E897a-w'	M3	L7	A13
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E899a-w'	M3	L7	A15
E900a-w'	M3	L7	A16
E901a-w'	M3	L7	A17
E902a-w'	M3	L7	A18
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E906a-w'	M3	L7	A22
E907a-w'	M3	L7	A23
E908a-w'	M3	L7	A24
E909a-w'	M3	L7	A25
E910a-w'	M3	L7	A26
E911a-w'	M3	L8	A1
E912a-w'	M3	L8	A2
E913a-w'	M3	L8	A3
E914a-w'	M3	L8	A4
E915a-w'	M3	L8	A5
E916a-w'	M3	L8	A6
E917a-w'	M3	L8	A7
E918a-w'	M3	L8	A8
E919a-w'	M3	L8	A9

E920a-w'	M3	L8	A10
E921a-w'	M3	L8	A11
E922a-w'	M3	L8	A12
E923a-w'	M3	L8	A13
E924a-w'	M3	L8	A14
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E928a-w'	M3	L8	A18
E929a-w'	M3	L8	A19
E930a-w'	M3	L8	A20
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E932a-w'	M3	L8	A22
E933a-w'	M3	L8	A23
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E935a-w'	M3	L8	A25
E936a-w'	M3	L8	A26
E937a-w'	M3	L9	A1
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E947a-w'	M3	L9	A11
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E949a-w'	M3	L9	A13
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E951a-w'	M3	L9	A15
E952a-w'	M3	L9	A16
E953a-w'	M3	L9	A17
E954a-w'	M3	L9	A18
E955a-w'	M3	L9	A19
E956a-w'	M3	L9	A20
E957a-w'	M3	L9	A21
E958a-w'	M3	L9	A22
E959a-w'	M3	L9	A23
E960a-w'	M3	L9	A24
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E963a-w'	M3	L10	A1
E964a-w'	M3	L10	A2

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E966a-w'	M3	L10	A4
E967a-w'	M3	L10	A5
E968a-w'	M3	L10	A6
E969a-w'	M3	L10	A7
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E983a-w'	M3	L10	A21
E984a-w'	M3	L10	A22
E985a-w'	M3	L10	A23
E986a-w'	M3	L10	A24
E987a-w'	M3	L10	A25
E988a-w'	M3	L10	A26
E989a-w'	M3	L11	A1
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E999a-w'	M3	L11	A11
E1000a-w'	M3	L11	A12
E1001a-w'	M3	L11	A13
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E1003a-w'	M3	L11	A15
E1004a-w'	M3	L11	A16
E1005a-w'	M3	L11	A17
E1006a-w'	M3	L11	A18
E1007a-w'	M3	L11	A19
E1008a-w'	M3	L11	A20
E1009a-w'	M3	L11	A21

E1010a-w'	M3	L11	A22
E1011a-w'	M3	L11	A23
E1012a-w'	M3	L11	A24
E1013a-w'	M3	L11	A25
E1014a-w'	M3	L11	A26
E1015a-w'	M3	L12	A1
E1016a-w'	M3	L12	A2
E1017a-w'	M3	L12	A3
E1018a-w'	M3	L12	A4
E1019a-w'	M3	L12	A5
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E1035a-w'	M3	L12	A21
E1036a-w'	M3	L12	A22
E1037a-w'	M3	L12	A23
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E1039a-w'	M3	L12	A25
E1040a-w'	M3	L12	A26
E1041a-w'	M3	L13	A1
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E1043a-w'	M3	L13	A3
E1044a-w'	M3	L13	A4
E1045a-w'	M3	L13	A5
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E1047a-w'	M3	L13	A7
E1048a-w'	M3	L13	A8
E1049a-w'	M3	L13	A9
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E1051a-w'	M3	L13	A11
E1052a-w'	M3	L13	A12
E1053a-w'	M3	L13	A13
E1054a-w'	M3	L13	A14

E1055a-w'	M3	L13	A15
E1056a-w'	M3	L13	A16
E1057a-w'	M3	L13	A17
E1058a-w'	M3	L13	A18
E1059a-w'	M3	L13	A19
E1060a-w'	M3	L13	A20
E1061a-w'	M3	L13	A21
E1062a-w'	M3	L13	A22
E1063a-w'	M3	L13	A23
E1064a-w'	M3	L13	A24
E1065a-w'	M3	L13	A25
E1066a-w'	M3	L13	A26
E1067a-w'	M3	L14	A1
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E1072a-w'	M3	L14	A6
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E1074a-w'	M3	L14	A8
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E1077a-w'	M3	L14	A11
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E1079a-w'	M3	L14	A13
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E1081a-w'	M3	L14	A15
E1082a-w'	M3	L14	A16
E1083a-w'	M3	L14	A17
E1084a-w'	M3	L14	A18
E1085a-w'	M3	L14	A19
E1086a-w'	M3	L14	A20
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E1088a-w'	M3	L14	A22
E1089a-w'	M3	L14	A23
E1090a-w'	M3	L14	A24
E1091a-w'	M3	L14	A25
E1092a-w'	M3	L14	A26
E1093a-w'	M4	L1	A1
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E1095a-w'	M4	L1	A3
E1096a-w'	M4	L1	A4
E1097a-w'	M4	L1	A5
E1098a-w'	M4	L1	A6
E1099a-w'	M4	L1	A7

E1100a-w'	M4	L1	A8
E1101a-w'	M4	L1	A9
E1102a-w'	M4	L1	A10
E1103a-w'	M4	L1	A11
E1104a-w'	M4	L1	A12
E1105a-w'	M4	L1	A13
E1106a-w'	M4	L1	A14
E1107a-w'	M4	L1	A15
E1108a-w'	M4	L1	A16
E1109a-w'	M4	L1	A17
E1110a-w'	M4	L1	A18
E1111a-w'	M4	L1	A19
E1112a-w'	M4	L1	A20
E1113a-w'	M4	L1	A21
E1114a-w'	M4	L1	A22
E1115a-w'	M4	L1	A23
E1116a-w'	M4	L1	A24
E1117a-w'	M4	L1	A25
E1118a-w'	M4	L1	A26
E1119a-w'	M4	L2	A1
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E1121a-w'	M4	L2	A3
E1122a-w'	M4	L2	A4
E1123a-w'	M4	L2	A5
E1124a-w'	M4	L2	A6
E1125a-w'	M4	L2	A7
E1126a-w'	M4	L2	A8
E1127a-w'	M4	L2	A9
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E1139a-w'	M4	L2	A21
E1140a-w'	M4	L2	A22
E1141a-w'	M4	L2	A23
E1142a-w'	M4	L2	A24
E1143a-w'	M4	L2	A25
E1144a-w'	M4	L2	A26

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E1146a-w'	M4	L3	A2
E1147a-w'	M4	L3	A3
E1148a-w'	M4	L3	A4
E1149a-w'	M4	L3	A5
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E1154a-w'	M4	L3	A10
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E1161a-w'	M4	L3	A17
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E1167a-w'	M4	L3	A23
E1168a-w'	M4	L3	A24
E1169a-w'	M4	L3	A25
E1170a-w'	M4	L3	A26
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E1173a-w'	M4	L4	A3
E1174a-w'	M4	L4	A4
E1175a-w'	M4	L4	A5
E1176a-w'	M4	L4	A6
E1177a-w'	M4	L4	A7
E1178a-w'	M4	L4	A8
E1179a-w'	M4	L4	A9
E1180a-w'	M4	L4	A10
E1181a-w'	M4	L4	A11
E1182a-w'	M4	L4	A12
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E1188a-w'	M4	L4	A18
E1189a-w'	M4	L4	A19

E1190a-w'	M4	L4	A20
E1191a-w'	M4	L4	A21
E1192a-w'	M4	L4	A22
E1193a-w'	M4	L4	A23
E1194a-w'	M4	L4	A24
E1195a-w'	M4	L4	A25
E1196a-w'	M4	L4	A26
E1197a-w'	M4	L5	A1
E1198a-w'	M4	L5	A2
E1199a-w'	M4	L5	A3
E1200a-w'	M4	L5	A4
E1201a-w'	M4	L5	A5
E1202a-w'	M4	L5	A6
E1203a-w'	M4	L5	A7
E1204a-w'	M4	L5	A8
E1205a-w'	M4	L5	A9
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E1213a-w'	M4	L5	A17
E1214a-w'	M4	L5	A18
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E1233a-w'	M4	L6	A11
E1234a-w'	M4	L6	A12

E1235a-w'	M4	L6	A13
E1236a-w'	M4	L6	A14
E1237a-w'	M4	L6	A15
E1238a-w'	M4	L6	A16
E1239a-w'	M4	L6	A17
E1240a-w'	M4	L6	A18
E1241a-w'	M4	L6	A19
E1242a-w'	M4	L6	A20
E1243a-w'	M4	L6	A21
E1244a-w'	M4	L6	A22
E1245a-w'	M4	L6	A23
E1246a-w'	M4	L6	A24
E1247a-w'	M4	L6	A25
E1248a-w'	M4	L6	A26
E1249a-w'	M4	L7	A1
E1250a-w'	M4	L7	A2
E1251a-w'	M4	L7	A3
E1252a-w'	M4	L7	A4
E1253a-w'	M4	L7	A5
E1254a-w'	M4	L7	A6
E1255a-w'	M4	L7	A7
E1256a-w'	M4	L7	A8
E1257a-w'	M4	L7	A9
E1258a-w'	M4	L7	A10
E1259a-w'	M4	L7	A11
E1260a-w'	M4	L7	A12
E1261a-w'	M4	L7	A13
E1262a-w'	M4	L7	A14
E1263a-w'	M4	L7	A15
E1264a-w'	M4	L7	A16
E1265a-w'	M4	L7	A17
E1266a-w'	M4	L7	A18
E1267a-w'	M4	L7	A19
E1268a-w'	M4	L7	A20
E1269a-w'	M4	L7	A21
E1270a-w'	M4	L7	A22
E1271a-w'	M4	L7	A23
E1272a-w'	M4	L7	A24
E1273a-w'	M4	L7	A25
E1274a-w'	M4	L7	A26
E1275a-w'	M4	L8	A1
E1276a-w'	M4	L8	A2
E1277a-w'	M4	L8	A3
E1278a-w'	M4	L8	A4
E1279a-w'	M4	L8	A5

E1280a-w'	M4	L8	A6
E1281a-w'	M4	L8	A7
E1282a-w'	M4	L8	A8
E1283a-w'	M4	L8	A9
E1284a-w'	M4	L8	A10
E1285a-w'	M4	L8	A11
E1286a-w'	M4	L8	A12
E1287a-w'	M4	L8	A13
E1288a-w'	M4	L8	A14
E1289a-w'	M4	L8	A15
E1290a-w'	M4	L8	A16
E1291a-w'	M4	L8	A17
E1292a-w'	M4	L8	A18
E1293a-w'	M4	L8	A19
E1294a-w'	M4	L8	A20
E1295a-w'	M4	L8	A21
E1296a-w'	M4	L8	A22
E1297a-w'	M4	L8	A23
E1298a-w'	M4	L8	A24
E1299a-w'	M4	L8	A25
E1300a-w'	M4	L8	A26
E1301a-w'	M4	L9	A1
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E1306a-w'	M4	L9	A6
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E1316a-w'	M4	L9	A16
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E1321a-w'	M4	L9	A21
E1322a-w'	M4	L9	A22
E1323a-w'	M4	L9	A23
E1324a-w'	M4	L9	A24

E1325a-w'	M4	L9	A25
E1326a-w'	M4	L9	A26
E1327a-w'	M4	L10	A1
E1328a-w'	M4	L10	A2
E1329a-w'	M4	L10	A3
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E1344a-w'	M4	L10	A18
E1345a-w'	M4	L10	A19
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E1413a-w'	M4	L13	A9
E1414a-w'	M4	L13	A10

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E1418a-w'	M4	L13	A14
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E1456a-w'	M4	L14	A26
E1457a-w'	M5	L1	A1
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E1459a-w'	M5	L1	A3

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E1537a-w'	M5	L4	A3
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E1541a-w'	M5	L4	A7
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E1545a-w'	M5	L4	A11
E1546a-w'	M5	L4	A12
E1547a-w'	M5	L4	A13
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E1549a-w'	M5	L4	A15

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E1553a-w'	M5	L4	A19
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E1557a-w'	M5	L4	A23
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E1559a-w'	M5	L4	A25
E1560a-w'	M5	L4	A26
E1561a-w'	M5	L5	A1
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E1563a-w'	M5	L5	A3
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E1565a-w'	M5	L5	A5
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E1567a-w'	M5	L5	A7
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E1598a-w'	M5	L6	A12
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E1616a-w'	M5	L7	A4
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E1619a-w'	M5	L7	A7
E1620a-w'	M5	L7	A8
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E1638a-w'	M5	L7	A26
E1639a-w'	M5	L8	A1

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E1642a-w'	M5	L8	A4
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E1644a-w'	M5	L8	A6
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E1662a-w'	M5	L8	A24
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E1667a-w'	M5	L9	A3
E1668a-w'	M5	L9	A4
E1669a-w'	M5	L9	A5
E1670a-w'	M5	L9	A6
E1671a-w'	M5	L9	A7
E1672a-w'	M5	L9	A8
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E1684a-w'	M5	L9	A20

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E1688a-w'	M5	L9	A24
E1689a-w'	M5	L9	A25
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E1693a-w'	M5	L10	A3
E1694a-w'	M5	L10	A4
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E1698a-w'	M5	L10	A8
E1699a-w'	M5	L10	A9
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E1702a-w'	M5	L10	A12
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E1706a-w'	M5	L10	A16
E1707a-w'	M5	L10	A17
E1708a-w'	M5	L10	A18
E1709a-w'	M5	L10	A19
E1710a-w'	M5	L10	A20
E1711a-w'	M5	L10	A21
E1712a-w'	M5	L10	A22
E1713a-w'	M5	L10	A23
E1714a-w'	M5	L10	A24
E1715a-w'	M5	L10	A25
E1716a-w'	M5	L10	A26
E1717a-w'	M5	L11	A1
E1718a-w'	M5	L11	A2
E1719a-w'	M5	L11	A3
E1720a-w'	M5	L11	A4
E1721a-w'	M5	L11	A5
E1722a-w'	M5	L11	A6
E1723a-w'	M5	L11	A7
E1724a-w'	M5	L11	A8
E1725a-w'	M5	L11	A9
E1726a-w'	M5	L11	A10
E1727a-w'	M5	L11	A11
E1728a-w'	M5	L11	A12
E1729a-w'	M5	L11	A13

E1730a-w'	M5	L11	A14
E1731a-w'	M5	L11	A15
E1732a-w'	M5	L11	A16
E1733a-w'	M5	L11	A17
E1734a-w'	M5	L11	A18
E1735a-w'	M5	L11	A19
E1736a-w'	M5	L11	A20
E1737a-w'	M5	L11	A21
E1738a-w'	M5	L11	A22
E1739a-w'	M5	L11	A23
E1740a-w'	M5	L11	A24
E1741a-w'	M5	L11	A25
E1742a-w'	M5	L11	A26
E1743a-w'	M5	L12	A1
E1744a-w'	M5	L12	A2
E1745a-w'	M5	L12	A3
E1746a-w'	M5	L12	A4
E1747a-w'	M5	L12	A5
E1748a-w'	M5	L12	A6
E1749a-w'	M5	L12	A7
E1750a-w'	M5	L12	A8
E1751a-w'	M5	L12	A9
E1752a-w'	M5	L12	A10
E1753a-w'	M5	L12	A11
E1754a-w'	M5	L12	A12
E1755a-w'	M5	L12	A13
E1756a-w'	M5	L12	A14
E1757a-w'	M5	L12	A15
E1758a-w'	M5	L12	A16
E1759a-w'	M5	L12	A17
E1760a-w'	M5	L12	A18
E1761a-w'	M5	L12	A19
E1762a-w'	M5	L12	A20
E1763a-w'	M5	L12	A21
E1764a-w'	M5	L12	A22
E1765a-w'	M5	L12	A23
E1766a-w'	M5	L12	A24
E1767a-w'	M5	L12	A25
E1768a-w'	M5	L12	A26
E1769a-w'	M5	L13	A1
E1770a-w'	M5	L13	A2
E1771a-w'	M5	L13	A3
E1772a-w'	M5	L13	A4
E1773a-w'	M5	L13	A5
E1774a-w'	M5	L13	A6

E1775a-w'	M5	L13	A7
E1776a-w'	M5	L13	A8
E1777a-w'	M5	L13	A9
E1778a-w'	M5	L13	A10
E1779a-w'	M5	L13	A11
E1780a-w'	M5	L13	A12
E1781a-w'	M5	L13	A13
E1782a-w'	M5	L13	A14
E1783a-w'	M5	L13	A15
E1784a-w'	M5	L13	A16
E1785a-w'	M5	L13	A17
E1786a-w'	M5	L13	A18
E1787a-w'	M5	L13	A19
E1788a-w'	M5	L13	A20
E1789a-w'	M5	L13	A21
E1790a-w'	M5	L13	A22
E1791a-w'	M5	L13	A23
E1792a-w'	M5	L13	A24
E1793a-w'	M5	L13	A25
E1794a-w'	M5	L13	A26
E1795a-w'	M5	L14	A1
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E1797a-w'	M5	L14	A3
E1798a-w'	M5	L14	A4
E1799a-w'	M5	L14	A5
E1800a-w'	M5	L14	A6
E1801a-w'	M5	L14	A7
E1802a-w'	M5	L14	A8
E1803a-w'	M5	L14	A9
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E1809a-w'	M5	L14	A15
E1810a-w'	M5	L14	A16
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E1815a-w'	M5	L14	A21
E1816a-w'	M5	L14	A22
E1817a-w'	M5	L14	A23
E1818a-w'	M5	L14	A24
E1819a-w'	M5	L14	A25

E1820a-w'	M5	L14	A26
E1821a-w'	M6	L1	A1
E1822a-w'	M6	L1	A2
E1823a-w'	M6	L1	A3
E1824a-w'	M6	L1	A4
E1825a-w'	M6	L1	A5
E1826a-w'	M6	L1	A6
E1827a-w'	M6	L1	A7
E1828a-w'	M6	L1	A8
E1829a-w'	M6	L1	A9
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E1832a-w'	M6	L1	A12
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E1835a-w'	M6	L1	A15
E1836a-w'	M6	L1	A16
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E1838a-w'	M6	L1	A18
E1839a-w'	M6	L1	A19
E1840a-w'	M6	L1	A20
E1841a-w'	M6	L1	A21
E1842a-w'	M6	L1	A22
E1843a-w'	M6	L1	A23
E1844a-w'	M6	L1	A24
E1845a-w'	M6	L1	A25
E1846a-w'	M6	L1	A26
E1847a-w'	M6	L2	A1
E1848a-w'	M6	L2	A2
E1849a-w'	M6	L2	A3
E1850a-w'	M6	L2	A4
E1851a-w'	M6	L2	A5
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E1853a-w'	M6	L2	A7
E1854a-w'	M6	L2	A8
E1855a-w'	M6	L2	A9
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E1857a-w'	M6	L2	A11
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E1861a-w'	M6	L2	A15
E1862a-w'	M6	L2	A16
E1863a-w'	M6	L2	A17
E1864a-w'	M6	L2	A18

E1865a-w'	M6	L2	A19
E1866a-w'	M6	L2	A20
E1867a-w'	M6	L2	A21
E1868a-w'	M6	L2	A22
E1869a-w'	M6	L2	A23
E1870a-w'	M6	L2	A24
E1871a-w'	M6	L2	A25
E1872a-w'	M6	L2	A26
E1873a-w'	M6	L3	A1
E1874a-w'	M6	L3	A2
E1875a-w'	M6	L3	A3
E1876a-w'	M6	L3	A4
E1877a-w'	M6	L3	A5
E1878a-w'	M6	L3	A6
E1879a-w'	M6	L3	A7
E1880a-w'	M6	L3	A8
E1881a-w'	M6	L3	A9
E1882a-w'	M6	L3	A10
E1883a-w'	M6	L3	A11
E1884a-w'	M6	L3	A12
E1885a-w'	M6	L3	A13
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E1887a-w'	M6	L3	A15
E1888a-w'	M6	L3	A16
E1889a-w'	M6	L3	A17
E1890a-w'	M6	L3	A18
E1891a-w'	M6	L3	A19
E1892a-w'	M6	L3	A20
E1893a-w'	M6	L3	A21
E1894a-w'	M6	L3	A22
E1895a-w'	M6	L3	A23
E1896a-w'	M6	L3	A24
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E1898a-w'	M6	L3	A26
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E1902a-w'	M6	L4	A4
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E1904a-w'	M6	L4	A6
E1905a-w'	M6	L4	A7
E1906a-w'	M6	L4	A8
E1907a-w'	M6	L4	A9
E1908a-w'	M6	L4	A10
E1909a-w'	M6	L4	A11

E1910a-w'	M6	L4	A12
E1911a-w'	M6	L4	A13
E1912a-w'	M6	L4	A14
E1913a-w'	M6	L4	A15
E1914a-w'	M6	L4	A16
E1915a-w'	M6	L4	A17
E1916a-w'	M6	L4	A18
E1917a-w'	M6	L4	A19
E1918a-w'	M6	L4	A20
E1919a-w'	M6	L4	A21
E1920a-w'	M6	L4	A22
E1921a-w'	M6	L4	A23
E1922a-w'	M6	L4	A24
E1923a-w'	M6	L4	A25
E1924a-w'	M6	L4	A26
E1925a-w'	M6	L5	A1
E1926a-w'	M6	L5	A2
E1927a-w'	M6	L5	A3
E1928a-w'	M6	L5	A4
E1929a-w'	M6	L5	A5
E1930a-w'	M6	L5	A6
E1931a-w'	M6	L5	A7
E1932a-w'	M6	L5	A8
E1933a-w'	M6	L5	A9
E1934a-w'	M6	L5	A10
E1935a-w'	M6	L5	A11
E1936a-w'	M6	L5	A12
E1937a-w'	M6	L5	A13
E1938a-w'	M6	L5	A14
E1939a-w'	M6	L5	A15
E1940a-w'	M6	L5	A16
E1941a-w'	M6	L5	A17
E1942a-w'	M6	L5	A18
E1943a-w'	M6	L5	A19
E1944a-w'	M6	L5	A20
E1945a-w'	M6	L5	A21
E1946a-w'	M6	L5	A22
E1947a-w'	M6	L5	A23
E1948a-w'	M6	L5	A24
E1949a-w'	M6	L5	A25
E1950a-w'	M6	L5	A26
E1951a-w'	M6	L6	A1
E1952a-w'	M6	L6	A2
E1953a-w'	M6	L6	A3
E1954a-w'	M6	L6	A4

E1955a-w'	M6	L6	A5
E1956a-w'	M6	L6	A6
E1957a-w'	M6	L6	A7
E1958a-w'	M6	L6	A8
E1959a-w'	M6	L6	A9
E1960a-w'	M6	L6	A10
E1961a-w'	M6	L6	A11
E1962a-w'	M6	L6	A12
E1963a-w'	M6	L6	A13
E1964a-w'	M6	L6	A14
E1965a-w'	M6	L6	A15
E1966a-w'	M6	L6	A16
E1967a-w'	M6	L6	A17
E1968a-w'	M6	L6	A18
E1969a-w'	M6	L6	A19
E1970a-w'	M6	L6	A20
E1971a-w'	M6	L6	A21
E1972a-w'	M6	L6	A22
E1973a-w'	M6	L6	A23
E1974a-w'	M6	L6	A24
E1975a-w'	M6	L6	A25
E1976a-w'	M6	L6	A26
E1977a-w'	M6	L7	A1
E1978a-w'	M6	L7	A2
E1979a-w'	M6	L7	A3
E1980a-w'	M6	L7	A4
E1981a-w'	M6	L7	A5
E1982a-w'	M6	L7	A6
E1983a-w'	M6	L7	A7
E1984a-w'	M6	L7	A8
E1985a-w'	M6	L7	A9
E1986a-w'	M6	L7	A10
E1987a-w'	M6	L7	A11
E1988a-w'	M6	L7	A12
E1989a-w'	M6	L7	A13
E1990a-w'	M6	L7	A14
E1991a-w'	M6	L7	A15
E1992a-w'	M6	L7	A16
E1993a-w'	M6	L7	A17
E1994a-w'	M6	L7	A18
E1995a-w'	M6	L7	A19
E1996a-w'	M6	L7	A20
E1997a-w'	M6	L7	A21
E1998a-w'	M6	L7	A22
E1999a-w'	M6	L7	A23

E2000a-w'	M6	L7	A24
E2001a-w'	M6	L7	A25
E2002a-w'	M6	L7	A26
E2003a-w'	M6	L8	A1
E2004a-w'	M6	L8	A2
E2005a-w'	M6	L8	A3
E2006a-w'	M6	L8	A4
E2007a-w'	M6	L8	A5
E2008a-w'	M6	L8	A6
E2009a-w'	M6	L8	A7
E2010a-w'	M6	L8	A8
E2011a-w'	M6	L8	A9
E2012a-w'	M6	L8	A10
E2013a-w'	M6	L8	A11
E2014a-w'	M6	L8	A12
E2015a-w'	M6	L8	A13
E2016a-w'	M6	L8	A14
E2017a-w'	M6	L8	A15
E2018a-w'	M6	L8	A16
E2019a-w'	M6	L8	A17
E2020a-w'	M6	L8	A18
E2021a-w'	M6	L8	A19
E2022a-w'	M6	L8	A20
E2023a-w'	M6	L8	A21
E2024a-w'	M6	L8	A22
E2025a-w'	M6	L8	A23
E2026a-w'	M6	L8	A24
E2027a-w'	M6	L8	A25
E2028a-w'	M6	L8	A26
E2029a-w'	M6	L9	A1
E2030a-w'	M6	L9	A2
E2031a-w'	M6	L9	A3
E2032a-w'	M6	L9	A4
E2033a-w'	M6	L9	A5
E2034a-w'	M6	L9	A6
E2035a-w'	M6	L9	A7
E2036a-w'	M6	L9	A8
E2037a-w'	M6	L9	A9
E2038a-w'	M6	L9	A10
E2039a-w'	M6	L9	A11
E2040a-w'	M6	L9	A12
E2041a-w'	M6	L9	A13
E2042a-w'	M6	L9	A14
E2043a-w'	M6	L9	A15
E2044a-w'	M6	L9	A16

E2045a-w'	M6	L9	A17
E2046a-w'	M6	L9	A18
E2047a-w'	M6	L9	A19
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E2049a-w'	M6	L9	A21
E2050a-w'	M6	L9	A22
E2051a-w'	M6	L9	A23
E2052a-w'	M6	L9	A24
E2053a-w'	M6	L9	A25
E2054a-w'	M6	L9	A26
E2055a-w'	M6	L10	A1
E2056a-w'	M6	L10	A2
E2057a-w'	M6	L10	A3
E2058a-w'	M6	L10	A4
E2059a-w'	M6	L10	A5
E2060a-w'	M6	L10	A6
E2061a-w'	M6	L10	A7
E2062a-w'	M6	L10	A8
E2063a-w'	M6	L10	A9
E2064a-w'	M6	L10	A10
E2065a-w'	M6	L10	A11
E2066a-w'	M6	L10	A12
E2067a-w'	M6	L10	A13
E2068a-w'	M6	L10	A14
E2069a-w'	M6	L10	A15
E2070a-w'	M6	L10	A16
E2071a-w'	M6	L10	A17
E2072a-w'	M6	L10	A18
E2073a-w'	M6	L10	A19
E2074a-w'	M6	L10	A20
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E2077a-w'	M6	L10	A23
E2078a-w'	M6	L10	A24
E2079a-w'	M6	L10	A25
E2080a-w'	M6	L10	A26
E2081a-w'	M6	L11	A1
E2082a-w'	M6	L11	A2
E2083a-w'	M6	L11	A3
E2084a-w'	M6	L11	A4
E2085a-w'	M6	L11	A5
E2086a-w'	M6	L11	A6
E2087a-w'	M6	L11	A7
E2088a-w'	M6	L11	A8
E2089a-w'	M6	L11	A9

E2090a-w'	M6	L11	A10
E2091a-w'	M6	L11	A11
E2092a-w'	M6	L11	A12
E2093a-w'	M6	L11	A13
E2094a-w'	M6	L11	A14
E2095a-w'	M6	L11	A15
E2096a-w'	M6	L11	A16
E2097a-w'	M6	L11	A17
E2098a-w'	M6	L11	A18
E2099a-w'	M6	L11	A19
E2100a-w'	M6	L11	A20
E2101a-w'	M6	L11	A21
E2102a-w'	M6	L11	A22
E2103a-w'	M6	L11	A23
E2104a-w'	M6	L11	A24
E2105a-w'	M6	L11	A25
E2106a-w'	M6	L11	A26
E2107a-w'	M6	L12	A1
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E2109a-w'	M6	L12	A3
E2110a-w'	M6	L12	A4
E2111a-w'	M6	L12	A5
E2112a-w'	M6	L12	A6
E2113a-w'	M6	L12	A7
E2114a-w'	M6	L12	A8
E2115a-w'	M6	L12	A9
E2116a-w'	M6	L12	A10
E2117a-w'	M6	L12	A11
E2118a-w'	M6	L12	A12
E2119a-w'	M6	L12	A13
E2120a-w'	M6	L12	A14
E2121a-w'	M6	L12	A15
E2122a-w'	M6	L12	A16
E2123a-w'	M6	L12	A17
E2124a-w'	M6	L12	A18
E2125a-w'	M6	L12	A19
E2126a-w'	M6	L12	A20
E2127a-w'	M6	L12	A21
E2128a-w'	M6	L12	A22
E2129a-w'	M6	L12	A23
E2130a-w'	M6	L12	A24
E2131a-w'	M6	L12	A25
E2132a-w'	M6	L12	A26
E2133a-w'	M6	L13	A1
E2134a-w'	M6	L13	A2

E2135a-w'	M6	L13	A3
E2136a-w'	M6	L13	A4
E2137a-w'	M6	L13	A5
E2138a-w'	M6	L13	A6
E2139a-w'	M6	L13	A7
E2140a-w'	M6	L13	A8
E2141a-w'	M6	L13	A9
E2142a-w'	M6	L13	A10
E2143a-w'	M6	L13	A11
E2144a-w'	M6	L13	A12
E2145a-w'	M6	L13	A13
E2146a-w'	M6	L13	A14
E2147a-w'	M6	L13	A15
E2148a-w'	M6	L13	A16
E2149a-w'	M6	L13	A17
E2150a-w'	M6	L13	A18
E2151a-w'	M6	L13	A19
E2152a-w'	M6	L13	A20
E2153a-w'	M6	L13	A21
E2154a-w'	M6	L13	A22
E2155a-w'	M6	L13	A23
E2156a-w'	M6	L13	A24
E2157a-w'	M6	L13	A25
E2158a-w'	M6	L13	A26
E2159a-w'	M6	L14	A1
E2160a-w'	M6	L14	A2
E2161a-w'	M6	L14	A3
E2162a-w'	M6	L14	A4
E2163a-w'	M6	L14	A5
E2164a-w'	M6	L14	A6
E2165a-w'	M6	L14	A7
E2166a-w'	M6	L14	A8
E2167a-w'	M6	L14	A9
E2168a-w'	M6	L14	A10
E2169a-w'	M6	L14	A11
E2170a-w'	M6	L14	A12
E2171a-w'	M6	L14	A13
E2172a-w'	M6	L14	A14
E2173a-w'	M6	L14	A15
E2174a-w'	M6	L14	A16
E2175a-w'	M6	L14	A17
E2176a-w'	M6	L14	A18
E2177a-w'	M6	L14	A19
E2178a-w'	M6	L14	A20
E2179a-w'	M6	L14	A21

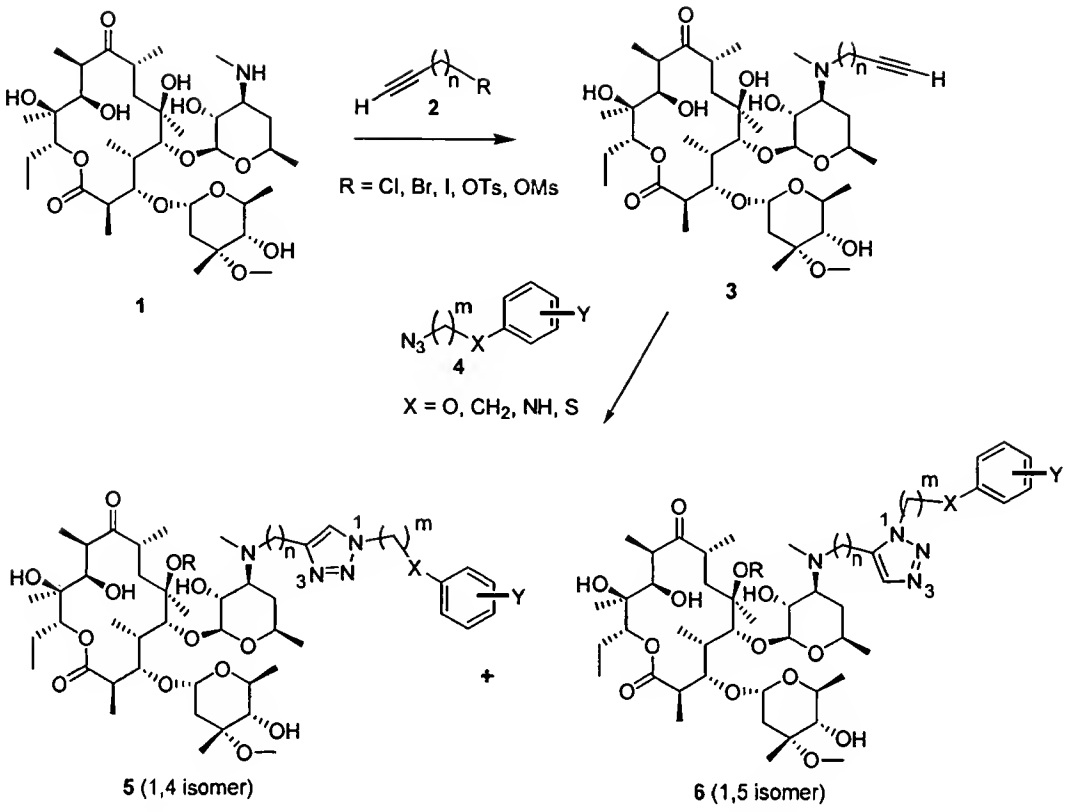
E2180a-w'	M6	L14	A22
E2181a-w'	M6	L14	A23
E2182a-w'	M6	L14	A24
E2183a-w'	M6	L14	A25
E2184a-w'	M6	L14	A26

3. Synthesis of the Compounds of the Invention

The invention provides methods for making the compounds of the invention. The following schemes depict exemplary chemistries available for synthesizing the compounds of the invention.

Scheme 1 illustrates the synthesis of triazole compounds of type **5** and **6**. Erythromycin can be N-demethylated as described in the art (U.S. Patent No. 3,725,385; Flynn *et al.* (1954) J. AM. CHEM. SOC. 76: 3121; Ku *et al.* (1997) BIOORG. MED. CHEM. LETT. 7: 1203; Stenmark *et al.* (2000) J. ORG. CHEM. 65: 3875) to afford secondary amine **1**. Alkylation of **1** with electrophiles of type **2** yields alkynes of type **3** containing a variable linker of appropriate length between the nitrogen atom and the alkyne group. Cycloaddition of azides of type **4** with alkynes **3** generates two regioisomeric triazole products. The reaction can be thermally catalyzed, or a number of catalysts could be added to facilitate the reaction (such as, but not limited to, copper (I) iodide: see Tornoe, C.W. *et al.* (2002) J. ORG. CHEM. 67: 3057). The major isomer (for steric reasons) is the "anti" isomer **5**, a 1,4 disubstituted triazole. The minor component is the "syn" isomer **6**, a 1,5 disubstituted triazole.

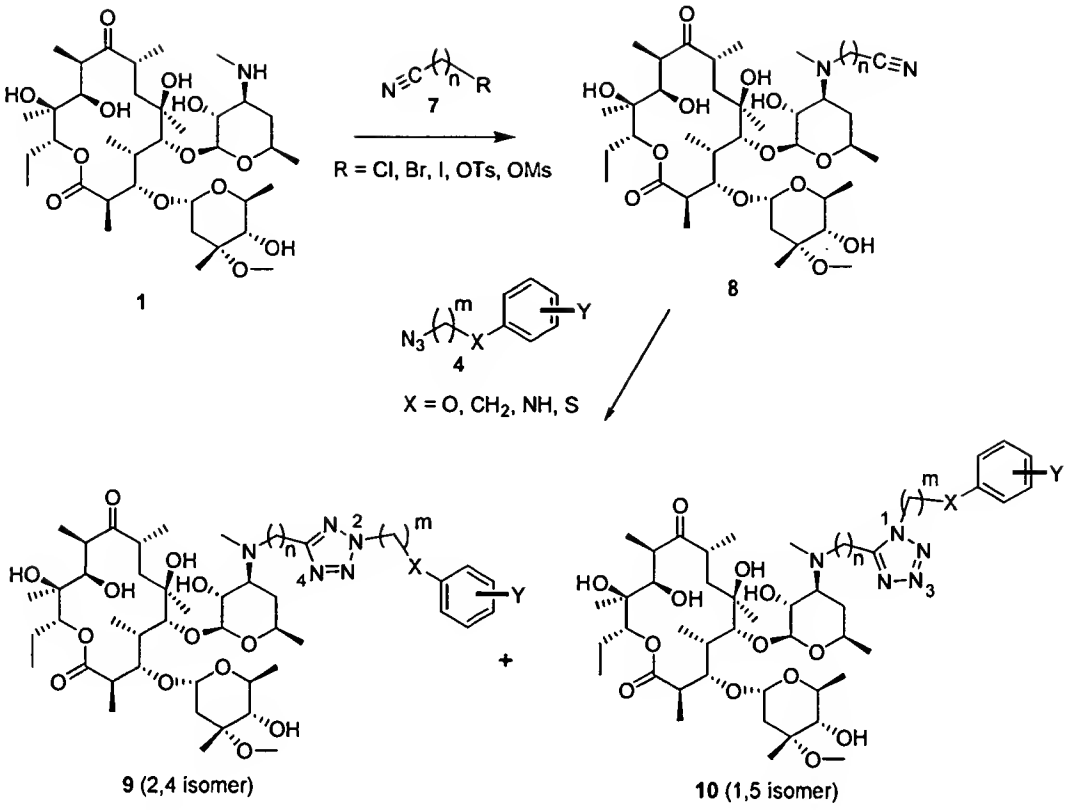
Scheme 1



It is to be understood that other macrolide compounds such as, but not limited to, azithromycin and clarithromycin, could be N-demethylated and serve as starting materials for the chemistry exemplified in Scheme 1. Target compounds derived from such alternate macrolide precursors are to be considered within the scope of the present invention.

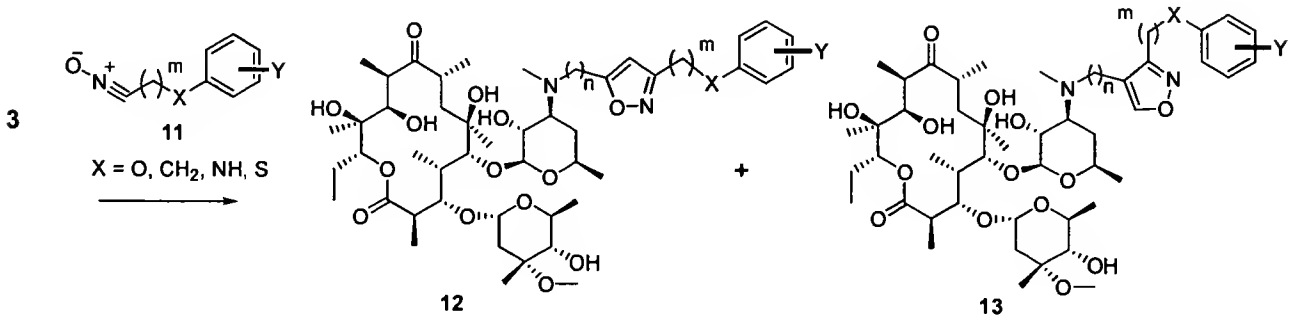
Scheme 2 illustrates the synthesis of exemplary tetrazole derivatives of the present invention. Amine **1** (or alternate macrolide amines) can be alkylated with nitrile-containing electrophiles of type **7** to afford macrolide nitrile intermediates of type **8**. Cycloaddition reactions of nitriles **8** with azides of type **4** may lead to two regioisomeric tetrazoles; the 2,4-disubstituted tetrazoles of type **9** (the expected major product), and the 1,5 isomers of type **10**.

Scheme 2



Scheme 3 depicts the synthesis of isoxazole derivatives of the present invention. Alkynes **3** can be treated with nitrile oxides of type **11** to afford regioisomeric cycloadducts **12** and **13**. The major isomer should again be the "anti" derivative **12** based on steric factors.

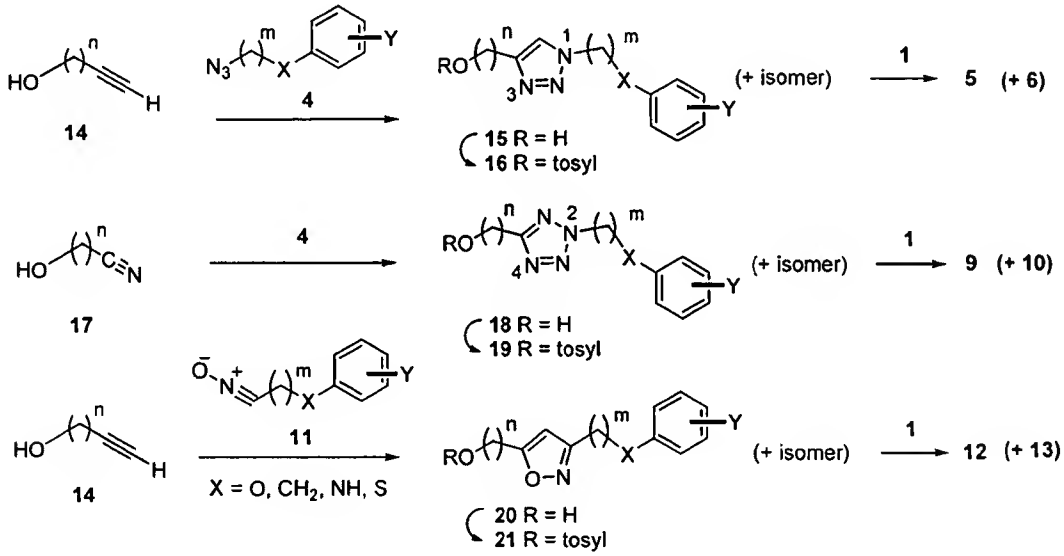
Scheme 3



An alternate approach to derivatives of type **5**, **6**, **9**, **10**, **12**, and **13** is illustrated by Scheme 4. Acetylenic alcohols of type **14** can be treated with azides **4** to yield intermediate alcohol **15** (along with a minor amount of the regioisomeric triazole). Tosylation of **15** will

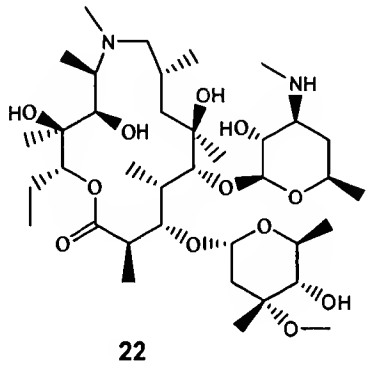
provide tosylates **16** which can serve as alkylating agents for macrolide amines of type **1** to afford targets **5** (and its isomer **6**). (It will be appreciated that other sulfonate derivatives or halides could be formed from intermediate alcohol **15**, and these would be useful as electrophiles for the alkylation of macrolide amines such as **1** to afford compounds of the invention.) Hydroxyalkyl nitriles of type **17** (where n is not equal to 1) can undergo cycloaddition with azides **4** to afford tetrazole intermediate **18** (along with a minor amount of the regioisomeric tetrazole). Tosylation of **18** to give **19** can again be followed by alkylation with amines of type **1** to yield derivative **9** (and its isomer **10**). In an analogous fashion, acetylenes **14** can be converted to isoxazoles **20** (and its isomer). An appropriate electrophile derived from **20** can then alkylate amines **1** to afford target **12** (and its isomer **13**).

Scheme 4

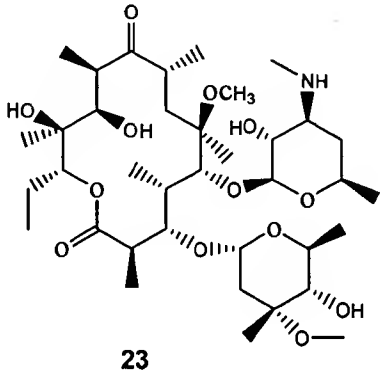


Other starting materials for the synthesis of compounds of the present invention are readily synthesizable. For example, des-methyl macrolide amines **22** and **23** can be prepared from azithromycin and clarithromycin respectively, using the same procedure for the synthesis of **1** from erythromycin. Ketolide derivatives (C-3 keto compounds synthesized from macrolides) of the present invention can be prepared by chemistry such as that shown in Scheme 5. Clarithromycin-derived amine **23** is alkylated with tosylate **24** to afford alkyne **25**. The cladinose sugar at C-3 is hydrolyzed to afford the C-3 hydroxy intermediate **26**, which is then selectively acetylated on the hydroxyl of the aminosaccharide group to yield **27**. Oxidation of **27**

yields C-3 keto derivative **28** which is then deacylated to provide alkyne **29**. Alkyne **29** can be exposed to the chemistry of Schemes 1 and 3 above to deliver triazole and isoxazole compounds of the present invention that have C-3 keto clarithromycin-derived structures. It will be understood that alkylation of **23** with electrophiles of type **7**, and then exposure of the product nitriles to the chemistry shown in Schemes 5 and 2, will yield tetrazoles that have C-3 keto clarithromycin-derived structures. Additionally, C-3 keto azithromycin and erythromycin intermediates could be prepared from **1** and **22** using the chemistry of Scheme 5, and subsequently serve as starting materials for compounds of the present invention.

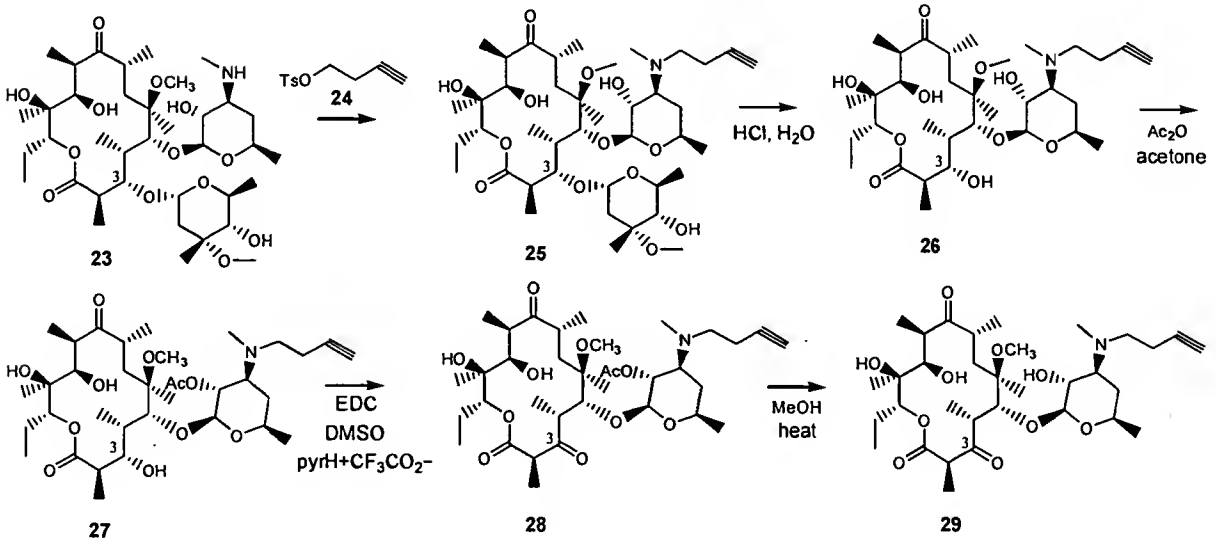


22



23

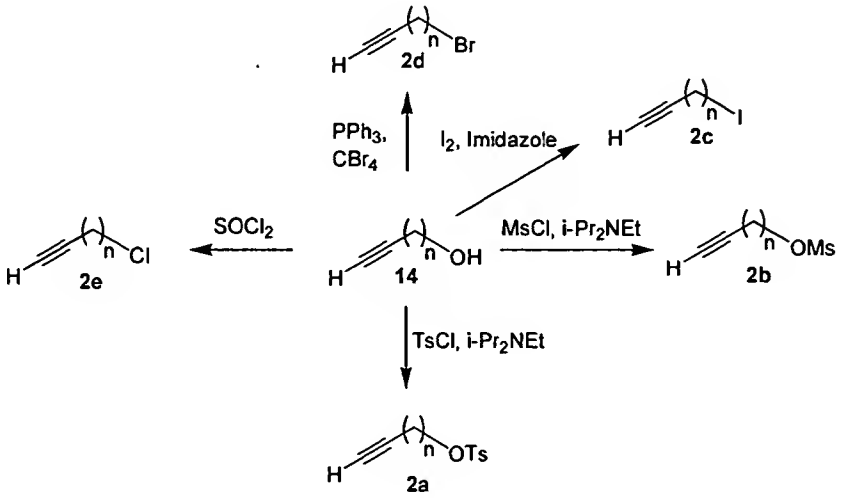
Scheme 5



Acetylenes of type **2**, used to synthesize the linker groups of the present invention, can be derived from commercially available haloalkyl acetylenes such as propargyl

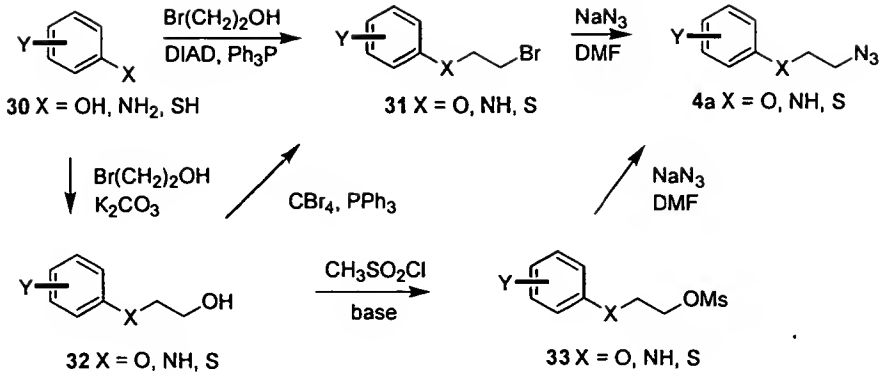
bromide, or they can be readily synthesized from available hydroxyalkyl acetylenes using chemistry well known in the art. Scheme 6 illustrates how they can be synthesized from available hydroxyalkyl acetylenes of type **14** using simple chemistry well known in the art.

Scheme 6

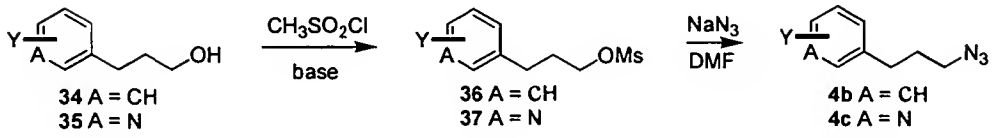


Intermediate azides of type **4** used to make compounds of the present invention can be synthesized using the methods exemplified in Schemes 7 and 8. Phenols, anilines, and thiophenols of type **30** can undergo Mitsunobu etherification processes with α,ω-halo alcohols (such as, but not limited to, 2-bromoethanol) to generate halides of type **31**. Displacement of the halogen with sodium azide yields azides **4a**. Alternatively, direct alkylation of intermediates **30** with α,ω-halo alcohols yields alcohols of type **32**, which can be converted to halides **31** or converted to a sulfonate derivative such as **33**, for subsequent azide displacement to afford azides **4a**. Arylpropanols of type **34**, and pyridylpropanols of type **35**, can be converted to azides **4b** and **4c** via sulfonates such as **36** and **37**. It will be appreciated that pyridyl derivatives with alternate substitution patterns (ortho and para), and alternate chain-lengths between the aryl moiety and the azide group can also be made using chemistry known in the art. It is intended that all such isomers and homologues are within the scope of the present invention.

Scheme 7

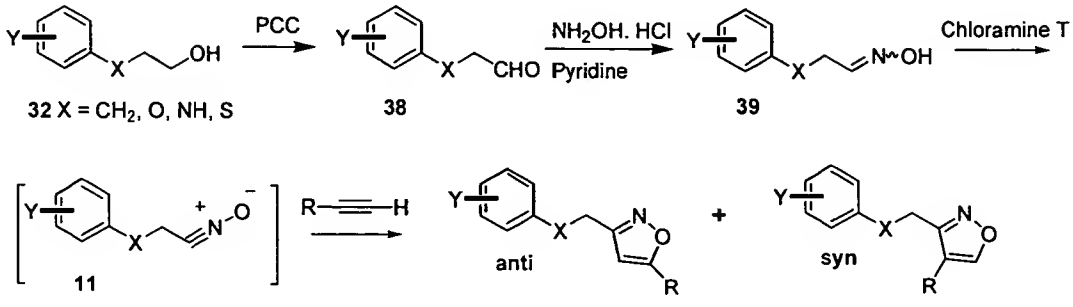


Scheme 8



Nitrile oxides of type **11** used to make compounds of the present invention can be synthesized using the method exemplified in Scheme 9. Substituted arylalkanols of type **32** (or pyridylalkanols) of various chain length between the aryl moiety and the alcohol group can be oxidized to aldehydes **38**. Conversion of the aldehyde to oximes **39** can be followed by conversion to intermediate nitrile oxides **11** using chloramine T (or other reagents used in combination with organic amine bases such as N-bromosuccinimide, N-chlorosuccinimide, t-butyl hypochlorite, lead tetraacetate etc.). The reaction to form the nitrile oxide can be run in the presence of an appropriate alkyne to trap the unstable intermediates **11** directly, affording a mixture of anti and syn isoxazole products.

Scheme 9



4. Characterization of Compounds of the Invention

Compounds designed, selected and/or optimized by methods described above, once produced, may be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules may be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity. Furthermore, high-throughput screening may be used to speed up analysis using such assays. As a result, it may be possible to rapidly screen the molecules described herein for activity, for example, as anti-cancer, anti-bacterial, anti-fungal, anti-parasitic or anti-viral agents. Also, it may be possible to assay how the compounds interact with a ribosome or ribosomal subunit and/or are effective as modulators (for example, inhibitors) of protein synthesis using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) High Throughput Screening, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

(1) *Surface Binding Studies.* A variety of binding assays may be useful in screening new molecules for their binding activity. One approach includes surface plasmon resonance (SPR) that can be used to evaluate the binding properties molecules of interest with respect to a ribosome, ribosomal subunit or a fragment thereof.

SPR methodologies measure the interaction between two or more macromolecules in real-time through the generation of a quantum-mechanical surface plasmon. One device, (BIAcore Biosensor RTM from Pharmacia Biosensor, Piscatawy, N.J.) provides a focused beam of polychromatic light to the interface between a gold film (provided as a disposable biosensor "chip") and a buffer compartment that can be regulated by the user. A 100 nm thick "hydrogel" composed of carboxylated dextran that provides a matrix for the covalent immobilization of analytes of interest is attached to the gold film. When the focused light interacts with the free electron cloud of the gold film, plasmon resonance is enhanced. The resulting reflected light is spectrally depleted in wavelengths that optimally evolved the resonance. By separating the reflected polychromatic light into its component wavelengths (by means of a prism), and determining the frequencies that are depleted, the BIAcore establishes an optical interface which accurately reports the behavior of the generated surface plasmon resonance. When designed as

above, the plasmon resonance (and thus the depletion spectrum) is sensitive to mass in the evanescent field (which corresponds roughly to the thickness of the hydrogel). If one component of an interacting pair is immobilized to the hydrogel, and the interacting partner is provided through the buffer compartment, the interaction between the two components can be measured in real time based on the accumulation of mass in the evanescent field and its corresponding effects of the plasmon resonance as measured by the depletion spectrum. This system permits rapid and sensitive real-time measurement of the molecular interactions without the need to label either component.

(2) *Fluorescence Polarization.* Fluorescence polarization (FP) is a measurement technique that can readily be applied to protein-protein, protein-ligand, or RNA-ligand interactions in order to derive IC_{50}s and Kds of the association reaction between two molecules. In this technique one of the molecules of interest is conjugated with a fluorophore. This is generally the smaller molecule in the system (in this case, the compound of interest). The sample mixture, containing both the ligand-probe conjugate and the ribosome, ribosomal subunit or fragment thereof, is excited with vertically polarized light. Light is absorbed by the probe fluorophores, and re-emitted a short time later. The degree of polarization of the emitted light is measured. Polarization of the emitted light is dependent on several factors, but most importantly on viscosity of the solution and on the apparent molecular weight of the fluorophore. With proper controls, changes in the degree of polarization of the emitted light depends only on changes in the apparent molecular weight of the fluorophore, which in-turn depends on whether the probe-ligand conjugate is free in solution, or is bound to a receptor. Binding assays based on FP have a number of important advantages, including the measurement of IC_{50}s and Kds under true homogenous equilibrium conditions, speed of analysis and amenity to automation, and ability to screen in cloudy suspensions and colored solutions.

(3) *Protein Synthesis.* It is contemplated that, in addition to characterization by the foregoing biochemical assays, the compound of interest may also be characterized as a modulator (for example, an inhibitor of protein synthesis) of the functional activity of the ribosome or ribosomal subunit.

Furthermore, more specific protein synthesis inhibition assays may be performed by administering the compound to a whole organism, tissue, organ, organelle, cell, a cellular or subcellular extract, or a purified ribosome preparation and observing its pharmacological and

inhibitory properties by determining, for example, its inhibition constant (IC_{50}) for inhibiting protein synthesis. Incorporation of ^{3}H leucine or ^{35}S methionine, or similar experiments can be performed to investigate protein synthesis activity. A change in the amount or the rate of protein synthesis in the cell in the presence of a molecule of interest indicates that the molecule is a modulator of protein synthesis. A decrease in the rate or the amount of protein synthesis indicates that the molecule is a inhibitor of protein synthesis.

Furthermore, the compounds may be assayed for anti-proliferative or anti-infective properties on a cellular level. For example, where the target organism is a microorganism, the activity of compounds of interest may be assayed by growing the microorganisms of interest in media either containing or lacking the compound. Growth inhibition may be indicative that the molecule may be acting as a protein synthesis inhibitor. More specifically, the activity of the compounds of interest against bacterial pathogens may be demonstrated by the ability of the compound to inhibit growth of defined strains of human pathogens. For this purpose, a panel of bacterial strains can be assembled to include a variety of target pathogenic species, some containing resistance mechanisms that have been characterized. Use of such a panel of organisms permits the determination of structure-activity relationships not only in regards to potency and spectrum, but also with a view to obviating resistance mechanisms. The assays may be performed in microtiter trays according to conventional methodologies as published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines (NCCLS. M7-A5-Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Fifth Edition. NCCLS Document M100-S12/M7 (ISBN 1-56238-394-9).

5. Formulation and Administration

The compounds of the invention may be useful in the prevention or treatment of a variety of human or other animal disorders, including for example, bacterial infection, fungal infections, viral infections, parasitic diseases, and cancer. It is contemplated that, once identified, the active molecules of the invention may be incorporated into any suitable carrier prior to use. The dose of active molecule, mode of administration and use of suitable carrier will depend upon the intended recipient and target organism. The formulations, both for veterinary and for human medical use, of compounds according to the present invention typically include such compounds in association with a pharmaceutically acceptable carrier.

The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers, in this regard, are intended to include any and all solvents, dispersion media, coatings, anti-bacterial and anti-fungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds (identified or designed according to the invention and/or known in the art) also can be incorporated into the compositions. The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy/microbiology. In general, some formulations are prepared by bringing the compound into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

A pharmaceutical composition of the invention should be formulated to be compatible with its intended route of administration. Examples of routes of administration include oral or parenteral, for example, intravenous, intradermal, inhalation, transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in Remington's Pharmaceutical Sciences, (Gennaro, A., ed.), Mack Pub., (1990). Formulations for parenteral administration can also include glycocholate for buccal administration, methoxysalicylate for rectal administration, or citric acid for vaginal administration. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Suppositories for rectal administration also can be prepared by mixing the drug with a non-

irritating excipient such as cocoa butter, other glycerides, or other compositions which are solid at room temperature and liquid at body temperatures. Formulations also can include, for example, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, and hydrogenated naphthalenes. Formulations for direct administration can include glycerol and other compositions of high viscosity. Other potentially useful parenteral carriers for these drugs include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration can contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Retention enemas also can be used for rectal delivery.

Formulations of the present invention suitable for oral administration may be in the form of: discrete units such as capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each containing a predetermined amount of the drug; a powder or granular composition; a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water emulsion or a water-in-oil emulsion. The drug may also be administered in the form of a bolus, electuary or paste. A tablet may be made by compressing or moulding the drug optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the drug in a free-flowing form such as a powder or granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered drug and suitable carrier moistened with an inert liquid diluent.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients. Oral compositions prepared using a fluid carrier for use as a mouthwash include the compound in the fluid carrier and are applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes;

a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the drug that may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the drug for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration, including eye treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream, ointment or soap. Particularly useful are carriers capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating solutions, such as pectin-containing formulations can be used.

For inhalation treatments, inhalation of powder (self-propelling or spray formulations) dispensed with a spray can, a nebulizer, or an atomizer can be used. Such formulations can be in the form of a fine powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling solution and spray formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics (*i.e.,* being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. For administration by inhalation, the compounds also can be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.,* a gas such as carbon dioxide, or a nebulizer.

Systemic administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants generally are known in the art, and include, for example, for transmucosal administration, detergents and bile salts. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds typically are formulated into ointments, salves, gels, or creams as generally known in the art.

The active compounds may be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can

be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

Oral or parenteral compositions can be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals. Furthermore, administration can be by periodic injections of a bolus, or can be made more continuous by intravenous, intramuscular or intraperitoneal administration from an external reservoir (*e.g.*, an intrvenous bag).

Where adhesion to a tissue surface is desired the composition can include the drug dispersed in a fibrinogen-thrombin composition or other bioadhesive. The compound then can be painted, sprayed or otherwise applied to the desired tissue surface. Alternatively, the drugs can be formulated for parenteral or oral administration to humans or other mammals, for example, in therapeutically effective amounts, *e.g.*, amounts that provide appropriate concentrations of the drug to target tissue for a time sufficient to induce the desired effect.

Where the active compound is to be used as part of a transplant procedure, it can be provided to the living tissue or organ to be transplanted prior to removal of tissue or organ from the donor. The compound can be provided to the donor host. Alternatively or, in addition, once removed from the donor, the organ or living tissue can be placed in a preservation solution containing the active compound. In all cases, the active compound can be administered directly to the desired tissue, as by injection to the tissue, or it can be provided systemically, either by oral or parenteral administration, using any of the methods and formulations described herein and/or known in the art. Where the drug comprises part of a tissue or organ preservation solution, any commercially available preservation solution can be used to advantage. For

example, useful solutions known in the art include Collins solution, Wisconsin solution, Belzer solution, Eurocollins solution and lactated Ringer's solution.

Active compound as identified or designed by the methods described herein can be administered to individuals to treat disorders (prophylactically or therapeutically). In conjunction with such treatment, pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

In therapeutic use for treating, or combating, bacterial infections in mammals, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level or tissue level of active component in the animal undergoing treatment which will be anti-microbially effective. The term "effective amount" is understood to mean that the compound of the invention is present in or on the recipient in an amount sufficient to elicit biological activity, for example, anti-microbial activity, anti-fungal activity, anti-viral activity, anti-parasitic activity, and/or anti-proliferative activity. Generally, an effective amount of dosage of active component will be in the range of from about 0.1 to about 100, more preferably from about 1.0 to about 50 mg/kg of body weight/day. The amount administered will also likely depend on such variables as the type and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the compound delivered, the formulation of the drug, the presence and types of excipients in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, for example, two to four times per day.

6. Examples

Some of the abbreviations used in the following experimental details of the synthesis of the examples are defined below:

hr=hour(s)

min=minute(s)

mol=mole(s)

mmol=millimole(s)

M=molar

μM=micromolar

g=gram(s)

μg=microgram(s)

rt=room temperature

L=liter(s)

mL=milliliter(s)

Et_2O=diethyl ether

THF=tetrahydrofuran

DMSO=dimethyl sulfoxide

EtOAc=ethyl acetate

Et_3N=triethylamine

CH_2Cl_2=methylene chloride

$CHCl_3$=chloroform

CCl_4=carbon tetrachloride

MeOH=methanol

DMF=dimethylformamide

BOC=t-butoxycarbonyl

TFA=trifluoroacetic acid

DBU=diazabicycloundecene

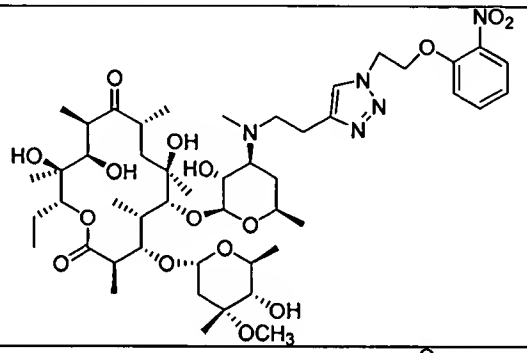
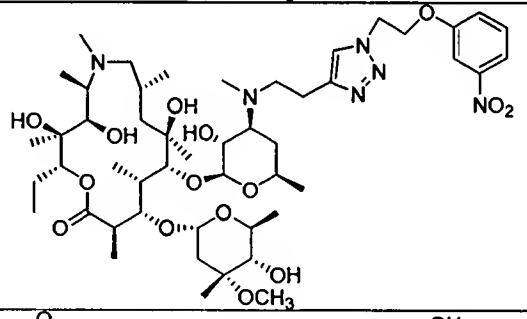
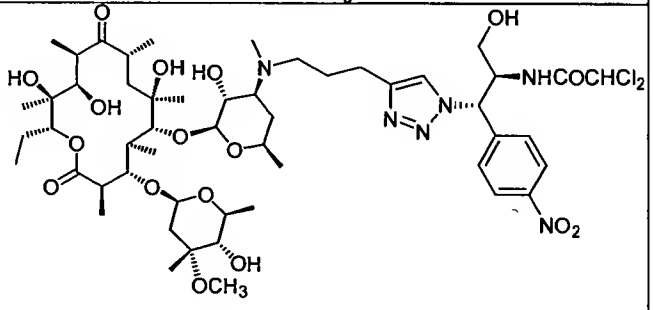
TBDPSCl=t-butyldiphenylchlorosilane

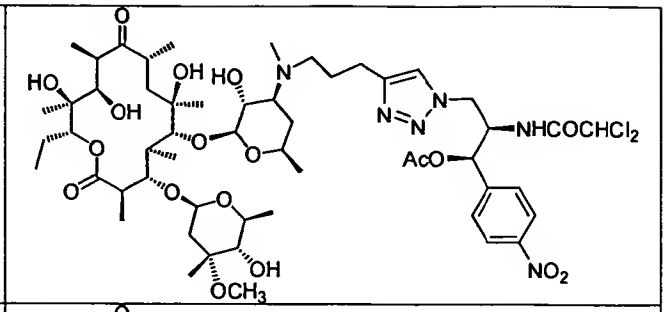
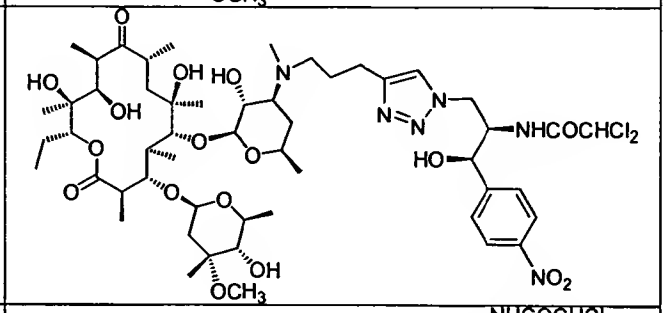
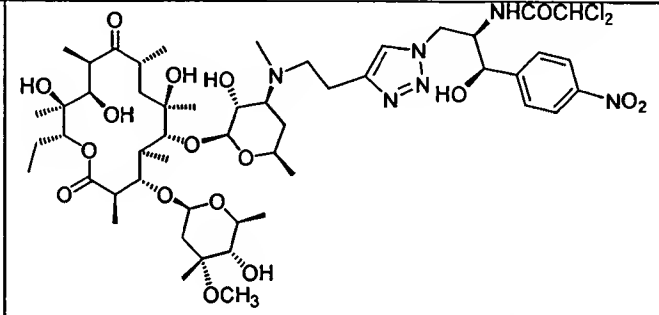
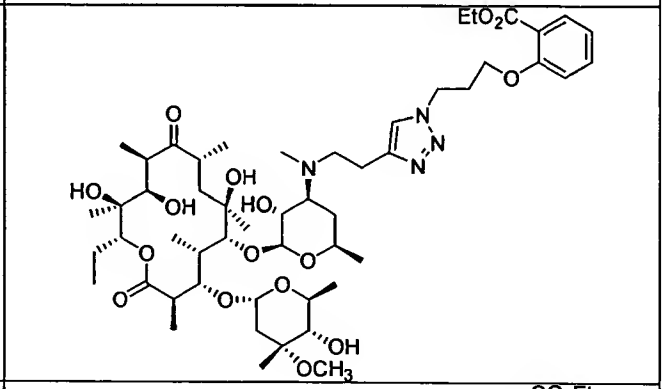
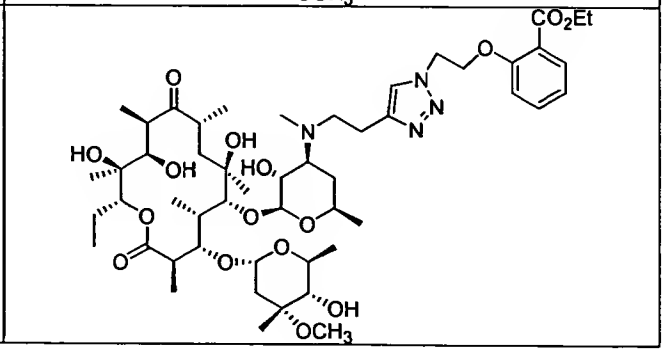
Hunig's Base=N,N-diisopropylethylamine

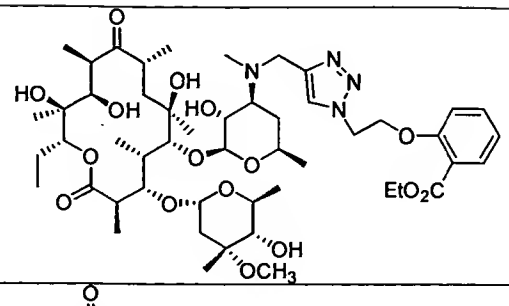
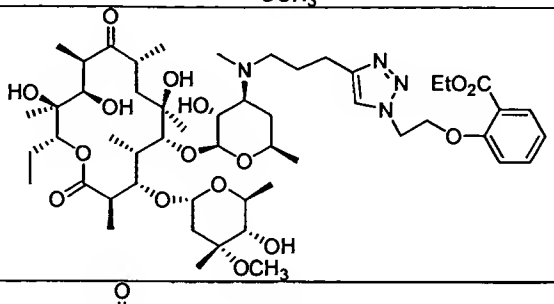
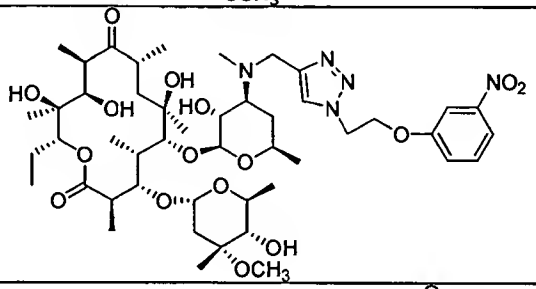
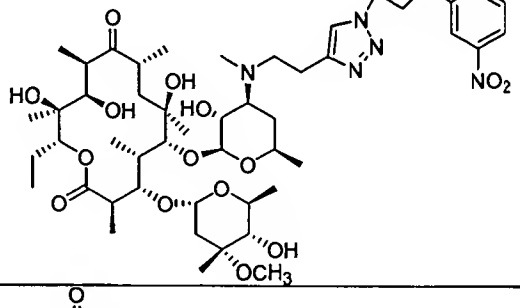
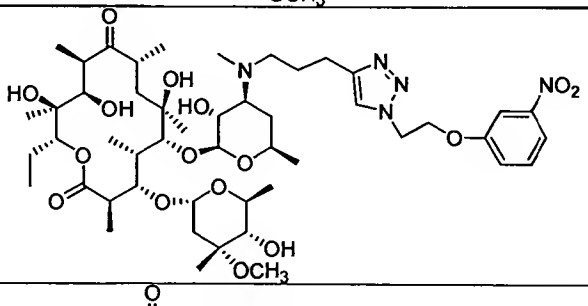
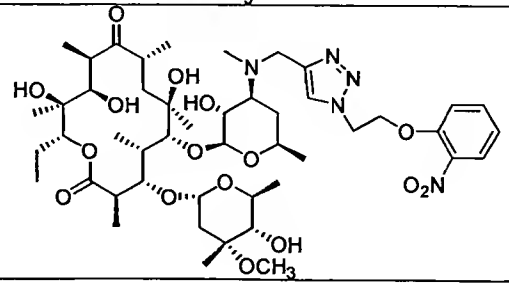
Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance 300 or Avance 500 spectrometer, or in some cases a GE-Nicolet 300 spectrometer. Common reaction solvents were either high performance liquid chromatography (HPLC) grade or American Chemical Society (ACS) grade, and anhydrous as obtained from the manufacturer unless otherwise noted. "Chromatography" or "purified by silica gel" refers to flash column chromatography using silica gel (EM Merck, Silica Gel 60, 230-400 mesh) unless otherwise noted.

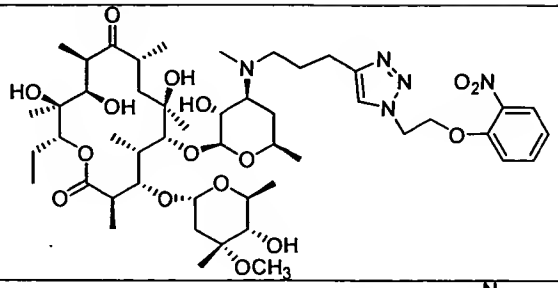
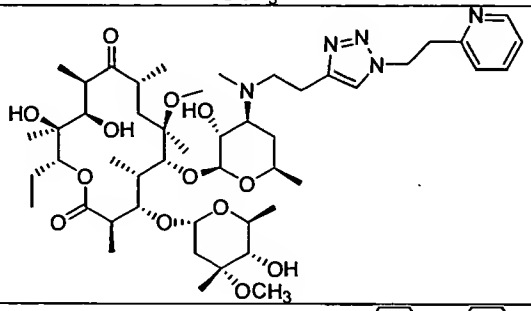
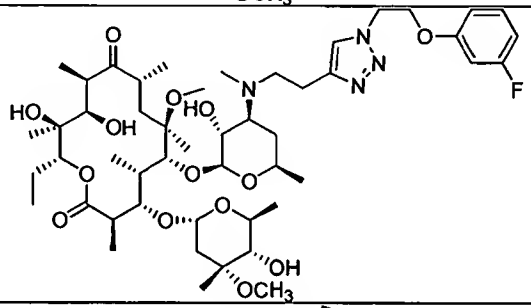
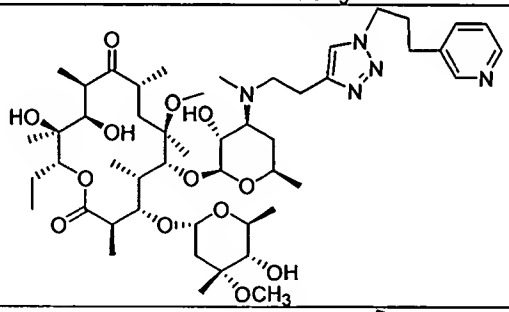
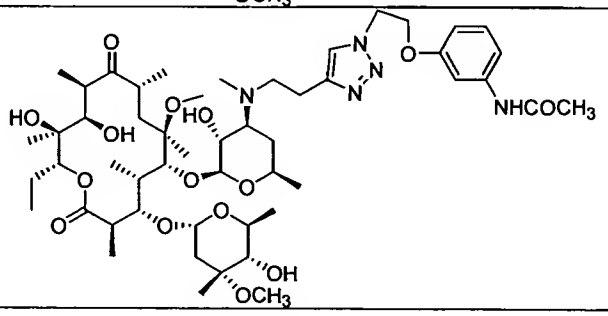
Compounds synthesized in accordance with the invention are listed in Table 3.

TABLE 3

Compound Number	Structure
100	
101	
102	

103	
104	
105	
106	
107	

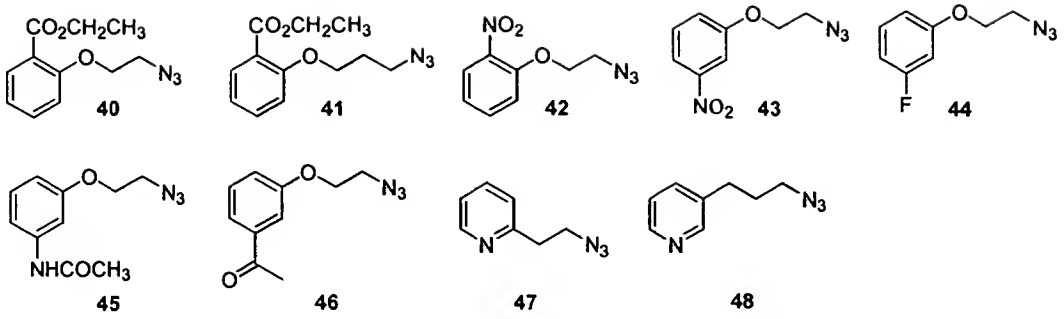
108	
109	
110	
111	
112	
113	

114	
115	
116	
117	
118	

Example 1 – Synthesis of Azides 40-48

The azides shown below in Scheme 10 were readily synthesized from available materials. Intermediates **40-46** were synthesized using the Mitsunobu approach illustrated by Scheme 7, and the pyridyl azides **47** and **48** were synthesized using the chemistry shown in Scheme 8.

Scheme 10



Synthesis of azide 40

To a mixture of ethyl salicylate (1.0 g, 6.0 mmol), bromoethanol (0.445 mL, 6.06 mmol), and triphenylphosphene (1.8 g, 6.9 mmol) in THF (10 mL) was added diisopropyl azodicarboxylate (DIAD, 1.40 mL, 6.60 mmol) at 0°C. The mixture was slowly warmed up to RT and stirred for 2 h. The reaction mixture was concentrated and redissolved in ethyl ether (50 mL). It was washed with brine (3 x 50 mL), dried (Na_2SO_4), concentrated and purified by flash chromatography (silica gel, 5% ethyl acetate in hexane) to yield 0.8 g of the intermediate bromoethyl ether. The bromoethyl ether (0.678 g, 2.4 mmol) was dissolved in DMF (5 mL) and sodium azide (0.473 g, 7.2 mmol) was added. The mixture was heated over an oil bath at 70°C for 2-3 h. The reaction mixture was diluted with ether (50 mL), washed with water (4 x 50 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to yield 0.52 g (89%) of pure azide **40**.

Synthesis of azides 41-46

Azides **41-46** were prepared from the starting phenols using the same procedure as that described for azide **40**.

Synthesis of azides 47 and 48

To a solution of 2-(2-hydroxyethyl)pyridine (2 g, 16.2 mmol) and diisopropylethylamine (5.6 mL, 32.4 mmol) in CH_2Cl_2 (40 mL) was added methanesulfonyl chloride (1.4 mL, 17.8 mmol) at 0°C. The mixture was stirred for 3 h at room temperature. The reaction was quenched

with water and diluted with CH_2Cl_2 (30 mL). The organic layer was washed with $NaHCO_3$ (2 x 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield 3.2 g of the crude mesylate which was of suitable purity to be used in subsequent reactions without purification. The above mesylate was converted to azide **47** using the same procedure used to synthesize azide **40** from the bromoethyl ether of ethyl salicylate.

Azide **48** was synthesized using the above procedure starting from 2-(3-hydroxypropyl)pyridine.

Example 2 – Synthesis of des(N-methyl)azithromycin 22

Azithromycin (0.80 g, 1.02 mmol) and sodium acetate (NaOAc) (0.712 g, 8.06 mmol) were dissolved in 80% aqueous MeOH (25 mL). The solution was kept at 50°C followed by addition of iodine (I_2) (0.272 g, 1.07 mmol) in three batches within 3 minutes. The reaction was maintained at a pH between 8 – 9 by adding 1N sodium hydroxide (NaOH) (1 mL) at 10 min and 45 minute intervals. The solution turned colorless within 45 minutes, however, stirring was continued for 2 hours. TLC (CH_2Cl_2/MeOH/NH_4OH 10:1:0.05) after 2 hours showed a single major product (Rf = 0.66). The reaction was cooled to room temperature, poured into H_2O (75 mL) containing NH_4OH (1.5 mL) and extracted with $CHCl_3$ (3 x 30 mL). The combined organic layer was washed with H_2O (30 mL) containing NH_4OH (1.5 mL), dried over Na_2SO_4 and the solvent evaporated to give a white residue. The crude was purified on silica gel column eluting with CH_2Cl_2/MeOH/NH_4OH 18:1:0.05 to 10:1:0.05 to provide amine **22** (0.41 g, 54.7%).

Example 3 – Synthesis of des(N-methyl)clarithromycin 23

To a mixture of clarithromycin (1.00 g, 1.3 mmol) and NaOAc•$3H_20$ (0.885 g, 6.5 mmol) was added MeOH-H_2O (20 mL, 4:1), and the mixture heated to 55-60°C. Iodine (0.330 g, 1.3 mmol) was added portionwise and the reaction stirred at 55-60°C for 3 h. The reaction mixture was poured into 50 mL $CHCl_3$ containing 1 mL ammonium hydroxide. It was extracted with $CHCl_3$ (4 x 50 mL), washed with water (70 mL) containing 5 mL ammonium hydroxide, dried (anhydrous Na_2SO_4), concentrated and purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 100:10:0.1) to afford **23**. Yield: 0.9g (92%).

Example 4 – Synthesis of Ketolide 29

Ketolide **29** was synthesized using the approach illustrated in Scheme 5 above.

Synthesis of tosylate 24

3-Butyn-1-ol (1.8 g, 25 mmol) was dissolved in CH_2Cl_2 (40 mL) and Et_3N (4.18 mL, 30 mmol). The solution was stirred at 0°C followed by addition of p-toluenesulfonyl chloride (5.05 g, 26.25 mmol). The reaction was allowed to warm to room temperature over a period of 1 hour and stirring was continued overnight. Thin layer chromatography (TLC) analysis (6:1 hexanes/EtOAc) after 20 hours of reaction showed a complete consumption of 3-butyn-1-ol. The precipitated triethylamine hydrochloride was filtered off and the filtrate washed with water (H_2O) (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated away to give **24** as a light-yellow oil (5.45 g, 97%). The crude oil was used without further purification; however, it could be purified on a silica gel column, first eluting with 8% EtOAc in hexanes followed by 40% EtOAc in hexanes.

Synthesis of alkyne 25

To a solution of *N*-desmethyl clarithromycin **23** (3.00 g, 4.08 mmol) and tosylate **24** (1.40 g, 6.13 mmol) in THF (45 mL) was added diisopropylethylamine (15 mL) and the mixture was refluxed for 48 h. The reaction mixture was concentrated under reduced pressure and redissolved in $CHCl_3$ (100 mL). The organic layer was washed with brine (3 x 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. After purification by flash chromatography (silica gel, 5% MeOH in $CHCl_3$), 2.50 g (78% yield) of pure product **25** was obtained. ^{1}HNMR (300 MHz, $CDCl_3$, partial): δ 0.85 (t, 3H), 2.25 (s, 3H), 3.00 (s, 3H), 3.20 (s, 1H), 3.25 (m, 1H), 3.30 (s, 3H), 3.50 (m, 1H), 3.55 (s, 1H), 3.65 (d, 1H), 3.75 (m, 3H), 4.00 (s, 1H), 4.05 (m, 1H), 4.45 (d, 1H), 4.95 (d, 1H), 5.10 (dd, 1H).

Synthesis of alcohol 26

To the alkyne **25** (0.700 g) was added 10 mL 0.9N HCl and the mixture was stirred for 4 h at room temperature. The reaction mixture was saturated with sodium chloride and was adjusted to pH 8 using aqueous NH_4OH solution. The solution was extracted with ethyl acetate (3 x 30 mL), dried (with Na_2SO_4), and concentrated under reduced pressure. Purification of the crude reaction mixture by flash chromatography (silica gel, 60% ethyl acetate in hexane) afforded 0.200 g (35% yield) of the descladinose derivative **26**. ^{1}HNMR (300 MHz, $CDCl_3$,

partial): δ 0.82 (t, 3H), 2.25 (s, 3H), 3.00 (s, 3H), 3.25 (dd, 1H), 3.55 (m, 2H), 3.70 (s, 1H), 3.85 (s, 1H), 3.95 (s, 1H), 4.40 (d, 1H), 5.15 (dd, 1H).

Synthesis of acetate 27

To a solution of **26** (0.200 g, 0.32 mmol) in acetone (2 mL) was added acetic anhydride (0.050 mL, 0.5 mmol) and the mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with saturated sodium bicarbonate (3 x 50 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel, 50% ethyl acetate in hexane) to yield 0.100 g (50% yield) of acetylated product **27**. ^{1}HNMR (300 MHz, $CDCl_3$, partial): δ 0.84 (t, 3H), 2.00 (s, 3H), 2.20 (s, 3H), 2.90 (s, 3H), 3.00 (q, 1H), 3.25 (s, 1H, 3.47 (m, 2H), 3.70 (bs, 1H), 3.82 (bs, 1H), 3.97 (s, 1H), 4.60 (d, 1H), 4.77 (dd, 1H), 5.15 (dd, 1H).

Synthesis of ketolide 28

To a solution of acetate **27** (0.090 g, 0.134 mmol), EDC•HCl (0.172 g, 0.90 mmol), and DMSO (0.171 mL, 2.41 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise a solution of pyridinium trifluoroacetate (0.174 g, 0.90 mmol) in CH_2Cl_2 (1 mL) at 15°C. The reaction mixture was slowly warmed up to room temperature and stirred for 3 h. The reaction was quenched with water (2 mL), and allowed to stir for 30 min. The mixture was then poured into $CHCl_3$ (50 mL), and the organic layer was washed with water (2 x 50 mL), dried (over anhydrous Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 30% ethyl acetate in hexane) to yield 0.070g (78%) of the ketoacetate **28**. MS (ESI): 668 ($M+H^+$), ^{1}HNMR (300 MHz, $CDCl_3$, partial): δ 0.86 (t, 3H), 2.00 (s, 3H), 2.24 (s, 3H), 2.70 (s, 3H), 2.95-3.10 (m, 1H), 3.15-3.05 (m, 1H), 3.45-3.65 (m, 1H), 3.80 (q, 1H), 3.90 (s, 1H), 4.28 (d, 1H), 4.40 (d, 1H), 4.76 (dd, 1H), 5.10 (dd, 1H).

Synthesis of ketolide 29

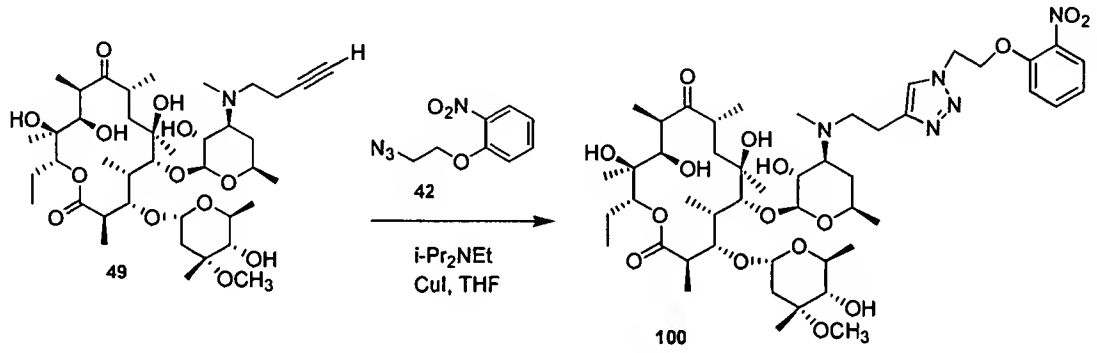
A solution of ketolide **28** (0.230 g) in MeOH (10 mL) was heated at 50°C for 48 h. The solvent was removed under reduced pressure to yield pure deacetylated product **29** (0.190 g, 88%). MS (ESI): 626 ($M+H^+$). ^{1}HNMR (300 MHz, $CDCl_3$, partial): δ 0.85 (t, 3H), 2.25 (s, 3H),

2.70 (s, 3H), 2.97 (q, 1H), 3.10 (t, 1H), 3.18 (dd, 1H), 3.5 (m, 1H), 3.80-3.97 (m, 2H), 4.32 (m, 2H), 5.15 (dd, 1H).

Example 5 – Synthesis of Compound 100

Scheme 11 depicts the general synthesis of the compounds of the invention. Alkyne **49** is treated with azide **42** in the presence of Hunig's base (i-Pr_2NEt) and copper (I) iodide in tetrahydrofuran to afford **100**.

Scheme 11



Synthesis of alkyne 49

Alkyne **49** was synthesized from des(N-methyl)erythromycin **1** and tosylate **24** using the procedure used to produce alkyne **25**.

Synthesis of Compound 100

To a solution of alkyne **49** (0.1 g, 0.13 mmol), azide **42** (0.054 g, 0.26 mmol) and diisopropylethylamine (0.680 mL, 3.9 mmol) in THF (2 mL) was added CuI (0.05 g, 0.26 mmol). The mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with $CHCl_3$ (50 mL) and washed with saturated NH_4Cl (3 x 50 mL) solution, dried (Na_2SO_4) and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel, 5% MeOH in 1:1 EtOAc/hexane) to yield **100** (0.1 g).

Example 6 – Synthesis of Compound 101

Synthesis of azithromycin-derived alkyne

The required azithromycin-derived alkyne was synthesized from des(N-methyl)azithromycin **22** and tosylate **24** using the same procedure described above for the synthesis of alkyne **25**.

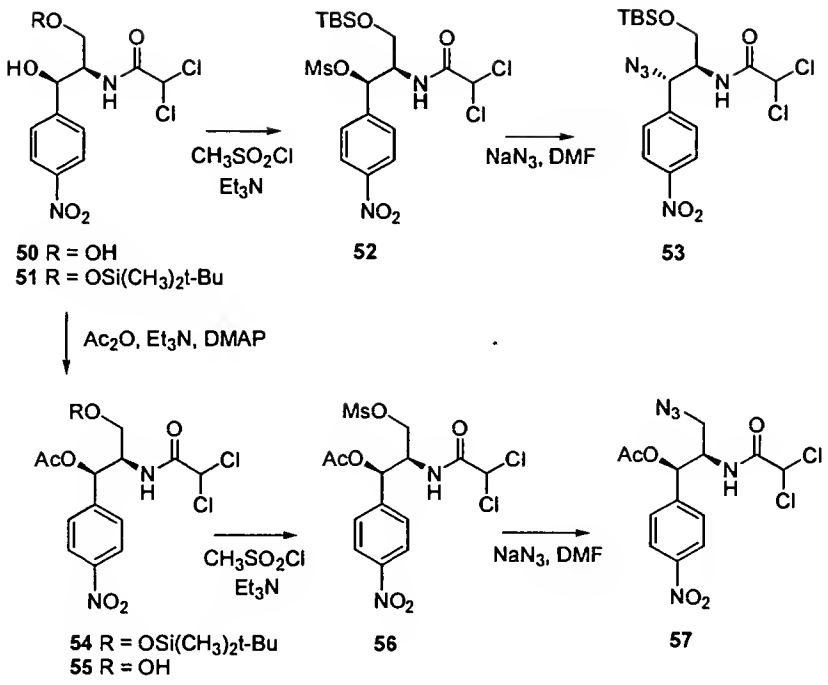
Synthesis of Compound 101

Azide **43** was synthesized from m-nitrophenol using the same procedure described above for the synthesis of azide **40**. Compound **101** was obtained by the reaction of azide **43** and the azithromycin-derived alkyne following the procedure reported above for the synthesis of **100**. Data for **101**: ^{1}H-NMR (300 MHz, $CDCl_3$, partial) δ 7.89 (dd, J = 8 Hz, 2 Hz, 1H), 7.74 (t, J = 2 Hz, 1H), 7.57 (s, 1H), 7.47 (t, J = 8 Hz, 1H), 7.24 (dd, J = 8 Hz, 2.5 Hz, 1H), 5.13 (d, J = 4 Hz, 1H), 4.68-4.82 (m, 3H), 4.47 (m, 3H), 4.30 (m, 1H), 4.09 (m, 1H), 3.68 (m, 2H), 3.34 (m, 5H), 0.92 (t, J = 8 Hz, 3H).

Example 7 – Synthesis of Azides 53 and 57

Scheme 12 depicts the synthesis of azides **53** and **57** required for the synthesis of **102**, **103**, **104** and **105**. Chloramphenicol **50** is silylated to afford alcohol **51** which is then converted to mesylate **52**. Displacement of the mesylate with sodium azide gives azide **53**. Silyl ether **51** is acetylated to afford acetate **54**, which can then be desilylated to provide alcohol **55**. The hydroxyl of **55** is mesylated to yield **56**, which is then converted to azide **57**.

Scheme 12



Synthesis of alcohol 51

To a mixture of chloramphenicol **50** (6.26 g, 20 mmol) and tert-butyldimethylsilyl chloride (3.32 g, 22 mmol) in CH_2Cl_2 (40 mL) was added imidazole (1.70 g, 25 mmol). After stirring at room temperature for 4 h, the solution was quenched with saturated $NaHCO_3$ solution. The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After purification by flash chromatography (silica gel, 6:1 hexane/ethyl acetate), 8.85 g of white crystalline **51** was obtained in a yield of 96%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.95 (s, 9H), 3.97 (m, 2H), 4.12 (m, 1H), 5.31 (s, 1H), 5.79 (s, 1H), 7.20 (d, J = 9 Hz, 1H), 7.55 (d, J = 9 Hz, 2H), 8.20 (d, J = 9 Hz, 2H).

Synthesis of mesylate 52

Methanesufonyl chloride (0.32 g, 2.75 mmol) was added dropwise to a solution of **51** (1.09 g, 2.5 mmol) and Et_3N (0.51 g, 5.0 mmol) in CH_2Cl_2 (5 mL) at 0°C. The mixture was kept stirring at 0°C for 2 h and at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc. The EtOAc solution was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford 1.22 g of **52** as light yellow oil. Yield: 95%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.90 (s, 9H), 2.90 (s,

3H), 3.36 (dd, J = 6, 11 Hz, 1H), 3.65 (dd, J = 5, 11 Hz, 1H), 4.32 (m, 1H), 5.80 (d, J = 7 Hz, 1H), 5.90 (s, 1H), 7.00 (d, J = 9 Hz, 1H), 7.58 (d, J = 9 Hz, 2H), 8.26 (d, J = 9 Hz, 2H).

Synthesis of azide 53

A mixture of mesylate **52** (1.32g, 2.5 mmol) and sodium azide (0.65g, 10 mmol) in DMF (5 ml) was stirred at 50-60°C for 5 h. The reaction was quenched with water. The solution was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuum. The crude product was purified by chromatography (silica gel, 15:1 hexane/ethyl acetate) to afford 0.75 g of light yellow oil **53**. Yield: 65%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.16 (s, 3H), 0.96 (s, 9H), 3.65 (dd, J = 3, 10 Hz, 1H), 4.06 (dd, J = 2, 11 Hz, 1H), 4.18 (m, 1H), 4.82 (d, J = 9 Hz, 1H), 5.68 (s, 1H), 6.89 (d, J = 9 Hz, 1H), 7.55 (d, J = 9 Hz, 2H), 8.23 (d, J = 9 Hz, 2H); MS (ESI) m/z 460 $(M-H)^+$.

Synthesis of acetate 54

Triethylamine (2.5 mL, 17.9 mmol) was added to a solution of **51** (3.3 g, 7.6 mmol), acetic anhydride (2.4 g, 23.3 mmol) and 4-dimethylaminopyridine (60 mg, 0.49 mmol) in CH_2Cl_2 (30 mL) at 0°C. After stirring at same temperature for 2 h, the reaction was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography (silica gel, 6:1 hexane/ethyl acetate) of crude product afforded 3.4 g of white crystalline **54**. Yield: 94%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.90 (s, 9H), 2.10 (s, 3H), 3.35 (dd, J = 3, 11 Hz, 1H), 3.60 (dd, J = 4, 11 Hz, 1H), 4.35 (m, 1H), 5.85 (s, 1H), 6.10 (d, J = 8 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.55 (d, J = 9 Hz, 2H), 8.20 (d, J = 9 Hz, 2H).

Synthesis of alcohol 55

To a solution of **54** (3.59 g, 7.5 mmol) in THF (50 mL) was added a solution of 1.0 M TBAF in THF (7.5 mL, 7.5 mmol). The reaction mixture was stirred at room temperature under argon atmosphere for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved with EtOAc and washed with brine. The organic phase was dried ($MgSO_4$), concentrated and purified by chromatography (silica gel, 4:1 hexane/ethyl acetate) to afford 2.40 g of light yellow oil **55**. Yield: 88%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 4.22 (m, 1H),

4.42 (m, 2H), 5.08 (s, 1H), 5.78 (s, 1H), 6.94 (d, J = 9 Hz, 1H), 7.53 (d, J = 9 Hz, 2H), 8.20 (d, J = 9 Hz, 2H).

Synthesis of mesylate 56

Triethylamine (1.8 mL, 12.7 mmol) was added to a solution of **55** (2.32 g, 6.36 mmol) and methanesulfonyl chloride (0.80 g, 7.0 mmol) in CH_2Cl_2 (20 mL) at 0°C. After stirring at 0°C for 2 h, the solvent was removed under reduced pressure, the residue was dissolved in EtOAc and washed with brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afford 2.8 g of **56** as light yellow oil. Yield: 99%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.00 (s, 3H), 4.12 (dd, J = 6, 12 Hz, 1H), 4.27 (dd, J = 6, 12 Hz, 1H), 4.65 (m, 1H), 5.89 (m, 2H), 6.96 (d, J = 9 Hz, 1H), 7.57 (d, J = 9 Hz, 2H), 8.25 (d, J = 9 Hz, 2H).

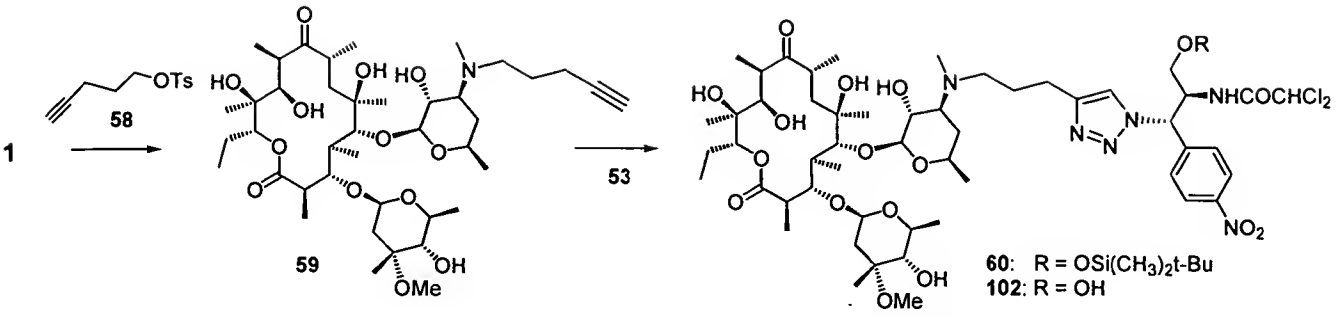
Synthesis of azide 57

The mixture of mesylate **56** (3.0 g, 6.8 mmol) and sodium azide (1.76 g, 27.1 mmol) in DMF (15 ml) was stirred at 60°C under argon atmosphere for 2 h. The reaction was quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and purified by chromatography (silica gel, 4:1 hexane/ethyl acetate) to afford 1.65 g light yellow solid **57**. Yield: 63%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3H), 4.06 (dd, J = 3, 11 Hz, 1H), 4.43 (m, 3H), 4.99 (d, J = 6 Hz, 1H), 5.86 (s, 1H), 6.95 (d, J = 5 Hz, 1H), 7.61 (d, J = 9 Hz, 2H), 8.28 (d, J = 9 Hz, 2H); MS (ESI) m/z 388 $(M-H)^+$.

Example 8 – Synthesis of Compound 102

Scheme 13 illustrates the synthesis of **102**. Des(N-methyl)erythromycin **1** is alkylated with tosylate **58** to afford alkyne **59**. Cycloaddition of **59** with azide **53** provides triazole **60** which is subsequently converted to **102** by desilylation.

Scheme 13



Synthesis of tosylate 58

Tosylate **58** was made from 4-pentyn-1-ol using the same procedure described for the synthesis of tosylate **24** above.

Synthesis of alkyne 59

Alkyne **59** was made from des(N-methyl)erythromycin **1** and tosylate **58** using the same procedure described for the synthesis of alkyne **25** above.

Synthesis of triazole 60

To a solution of **59** (50 mg, 0.063 mmol), azide **53** (46 mg, 0.098 mmol), and diisopropylethylamine (0.14 mL, 0.79 mmol) in THF (3 mL) was added CuI (24 mg, 0.13 mmol). The reaction mixture was stirred at room temperature for 12 h. The THF was removed under reduced pressure and the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under reduced pressure. The crude reaction mixture was purified by chromatography (silica gel, 40:1:0.1 CH_2Cl_2/MeOH/NH_3·H_2O) to afford triazole product **60** (52 mg) in a yield of 64%. ^{1}H-NMR (300 MHz, $CDCl_3$, partial) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.85 (t, 3H), 0.96 (s, 9H), 3.30 (s, 3H), 4.38 (d, 1H), 4.86 (d, 1H), 5.00 (d, 1H), 5.15 (t, 1H), 5.62 (s, 1H), 5.70 (d, 1H), 6.90 (d, 1H), 7.40 (s, 1H), 7.65 (d, 2H), 8.25 (d, 2H); MS (ESI) m/z 1247 $(M+H)^+$.

Synthesis of Compound 102

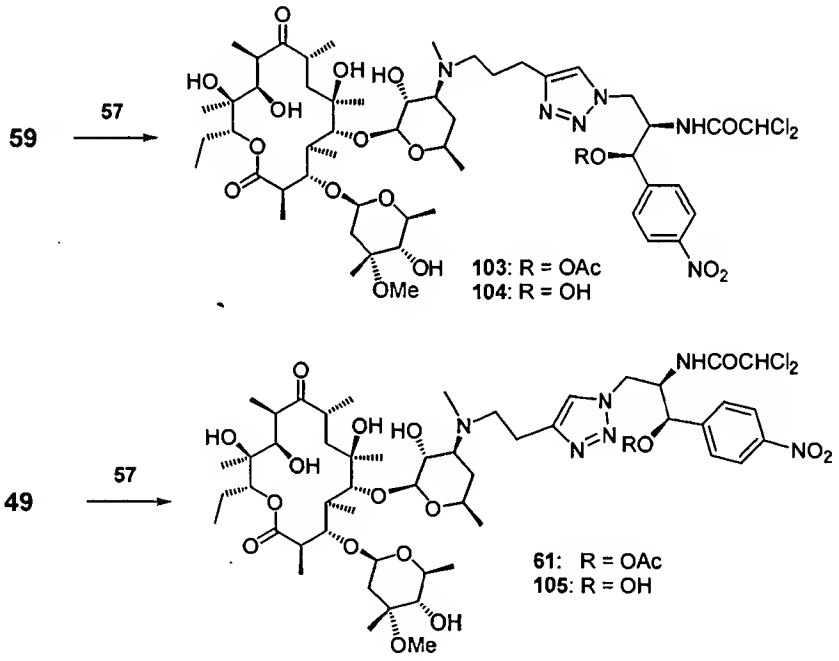
To a solution of **60** (60 mg, 0,048 mmol) in THF (1 mL) was added a solution of 1.0 M TBAF in THF (44 mg, 0.048 mmol). The reaction mixture was stirred at room temperature for 2 h. The THF was removed under reduced pressure and the residue was extracted with CH_2Cl_2,

washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. 35 mg of desired product **102** was obtained after purification by chromatography (silica gel, CH_2Cl_2/MeOH 10:1). Yield: 64%. ^{1}H-NMR (300 MHz, $CDCl_3$, partial) δ 0.85 (t, 3H), 3.30 (s, 3H), 4.40 (d, 1H), 4.90 (d, 1H), 5.20 (m, 2H), 5.86 (s, 1H), 6.10 (d, 1H), 7.75 (d, 2H), 8.20 (d, 2H); MS (ESI) m/z 1133 $(M+H)^+$.

Example 9 – Synthesis of Compounds 103, 104 and 105

Scheme 14 depicts the synthesis of **103**, **104** and **105**. Alkyne **59** is treated with azide **57** to afford acetate **103**. Acetate **103** is then hydrolyzed to yield **104**. Alkyne **49** is treated with azide **57** to afford acetate **61**. Acetate **61** is hydrolyzed to yield **105**.

Scheme 14



Synthesis of Compound 103

To a solution of **59** (79 mg, 0.1 mmol), azide **57** (47 mg, 0.12 mmol), and diisopropylethylamine (0.17 mL, 1.0 mmol) in THF (2 mL) was added CuI (38 mg, 0.2 mmol). The reaction mixture was stirred at room temperature under argon atmosphere for 12 h. The THF was removed under reduced pressure and the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under reduced pressure. The crude

reaction mixture was purified by chromatography (silica gel, 50:1 CH_2Cl_2/MeOH) to afford as a white foam **103** (90 mg) in a yield of 77%. ^{1}H-NMR (300 MHz, $CDCl_3$, partial) δ 0.85 (t, 3H), 2.06 (s, 3H), 3.31 (s, 3H), 4.42 (m, 2H), 4.89 (d, 1H), 5.04 (d, 1H), 5.20 (m, 1H), 5.83 (s, 1H), 6.04 (d, 1H), 7.23 (d, 1H), 7.47 (s, 1H), 7.65 (d, 2H), 8.23 (d, 2H); MS (ESI) m/z 1175 $(M + H)^+$.

Synthesis of Compound 104

To a solution of **103** (50 mg, 0.042 mmol) in methanol (2 mL) was added Et_3N (20 mg, 0.20 mmol). The reaction mixture was stirred at room temperature for 2 h. The organic solvents were removed under reduced pressure and the residue was purified by chromatography (silica gel, 10:1 CH_2Cl_2/MeOH) to afford as a white foam **104** (40.4 mg) in a yield of 84%. ^{1}H-NMR (300 MHz, $CDCl_3$, partial) δ 0.85 (t, 3H), 3.30 (s, 3H), 4.39 (d, 1H), 4.89 (d, 1H), 5.03 (m, 2H), 5.86 (s, 1H), 6.08 (d, 1H), 7.24 (d, 1H), 7.41 (s, 1H), 7.73 (d, 2H), 8.22 (d, 2H); MS (ESI) m/z 1133 $(M + H)^+$.

Synthesis of acetate 61

To a solution of **49** (116 mg, 0.15 mmol), azide **57** (70 mg, 0.18 mmol), and diisopropylethylamine (0.26 mL, 1.5 mmol) in THF (3 mL) was added CuI (57 mg, 0.3 mmol). The reaction mixture was stirred at room temperature under argon atmosphere for 3 h. The THF was removed under reduced pressure and the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under reduced pressure. The crude reaction mixture was purified by chromatography (silica gel, 40:1 CH_2Cl_2/MeOH) to afford white foam **61** (126 mg) in a yield of 72%. ^{1}H-NMR (300 MHz, $CDCl_3$, partial) δ 0.85 (t, 3H), 2.10 (s, 3H), 3.35 (s, 3H), 4.32 (m, 1H), 4.42 (d, 1H), 4.88 (d, 1H), 5.05 (m, 2H), 5.95 (s, 1H), 6.02 (d, 1H), 7.23 (d, 1H), 7.46 (s, 1H), 7.65 (d, 2H), 8.22 (d, 2H); MS (ESI) m/z 1161 $(M + H)^+$.

Synthesis of Compound 105

To a solution of **61** (110 mg, 0.094 mmol) in methanol (3 mL) was added Et_3N (50 mg, 0.50 mmol). The reaction mixture was stirred at room temperature for 3 h. The organic solvents were removed under reduced pressure and the residue was purified by chromatography (silica

gel, 20:1 CH_2Cl_2/MeOH) to afford white crystalline **105** (90 mg) in a yield of 85%. ^{1}H-NMR (300 MHz, $CDCl_3$, partial) δ 0.84 (t, 3H), 3.28 (s, 3H), 4.35 (d, 1H), 4.88 (d, 1H), 5.05 (m, 2H), 5.88 (s, 1H), 5.96 (d, 1H), 7.22 (d, 1H), 7.51 (s, 1H), 7.74 (d, 2H), 8.20 (d, 2H); MS (ESI) m/z 1119 $(M + H)^+$.

INCORPORATION BY REFERENCE

The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

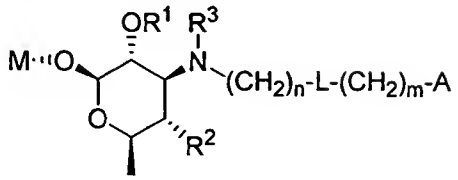
EQUIVALENTS

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

CLAIMS

What is claimed is:

1. A compound having the formula:



or a pharmaceutically acceptable salt, ester, or prodrug thereof,

wherein

M is a 14- or 15-membered macrolide linked via a macrocyclic ring carbon atom;

R^1 and R^3 independently are hydrogen, a C_{1-6} alkyl group, or a C_{1-6} acyl group;

R^2 is hydrogen or $-OR^1$;

n and m independently are 0, 1, 2, 3, 4, 5, or 6;

L is

(a) a sulfonamide group;

(b) a 5- or 6-membered saturated, unsaturated or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms, and optionally substituted with one or more chemical moieties selected from the groups consisting of:

(i) a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; and a nitro group; and

(ii) a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; a sulfonyl ester group, and a 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms;

wherein each of the moieties of (b)(ii) immediately above optionally is substituted with one or more chemical moieties selected from the group consisting of: a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; a nitro group, a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; a sulfonyl ester group; and a 5-

or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms; or

(c) $-D_p-(CH_2)_r-$(5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms) $-(CH_2)_{r'}-D_{p'}-$,

wherein

(i) D is a C_2 alkenyl group; an oxygen atom; an amine group; an amide group; a sulfur atom; a sulfoxide group; a sulfone group; a sulfonyl ester group; sulfonamide group; a carbonyl group; an imine group; an oxime group; a thioketone group; or a 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms as described in (b) immediately above;

(ii) p and p' independently are 0 or 1;

(iii) r and r' independently are 0, 1, 2, 3, or 4; and

(iv) the 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms is as described in (b) immediately above;

A is (a) a phenyl group; (b) a bicyclic aromatic group containing up to ten carbon atoms; (c) a 5- or 6-membered aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms; or (d) a bicyclic aromatic heterocyclic group containing up to ten carbon atoms and one or more oxygen, nitrogen, and sulfur atoms,

wherein each of (a)-(d) immediately above optionally is substituted with one or more chemical moieties selected from the groups consisting of:

(i) a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; and a nitro group; and

(ii) a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; and a sulfonyl ester group;

wherein each of the moieties of (ii) immediately above optionally is substituted with one or more chemical moieties selected from the group consisting of: a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; a nitro group, a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6}

alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; a sulfonyl ester group; and a 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms; and

(iii) a 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms;

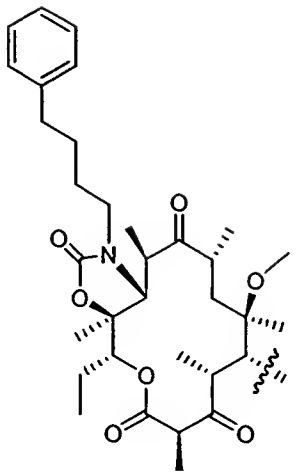
wherein the 5- or 6-membered saturated, unsaturated, or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms optionally is substituted with one or more chemical moieties selected from the groups consisting of:

(1) a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; and a nitro group; and

(2) a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; and a sulfonyl ester group;

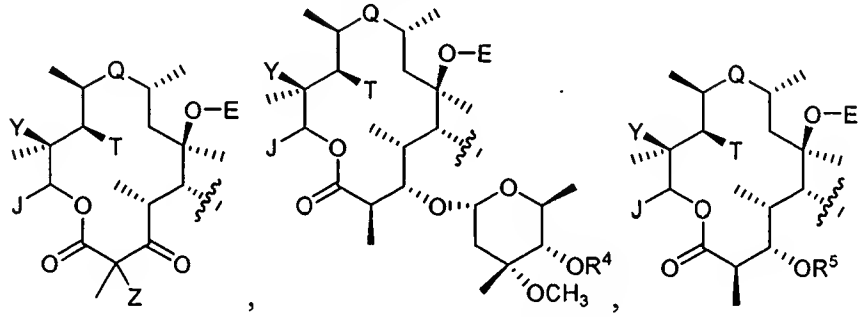
wherein each of the moieties of (iii)(2) immediately above optionally is substituted with one or more chemical moieties selected from the group consisting of: a halogen; a nitrile group; a mercapto group; a formyl group; a hydroxyl group; a nitro group, a C_{1-6} alkoxy group; a C_{1-6} alkoxycarbonyl group; a C_{1-6} alkylthio group; a C_{1-6} acyl group; a C_{1-6} alkyl group; a C_{2-6} alkenyl group; a C_{2-6} alkynyl group; an aryl group; an amine group; an amide group; a sulfonamide group; a sulfoxide group; a sulfone group; and a sulfonyl ester group;

provided that when M is



m is not 0 or 1.

2. The compound of claim 1 wherein M is selected from the group consisting of:



and pharmaceutically acceptable salts, esters and prodrugs thereof, wherein

(a) E is selected from the group consisting of: hydrogen, a C_{1-6}-alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, –C(O)-R^6, –C(O)-C_{1-6} alkyl group-R^6, -C(O)-C_{2-6} alkenyl group-R^6, –C(O)-C_{2-6} alkynyl group-R^6, -C_{1-6} alkyl group-G-R^6, -C_{2-6} alkenyl group-G-R^6; and –C_{2-6} alkynyl group-G-R^6;

wherein

(i) the C_{1-6}-alkyl group, the C_{2-6} alkenyl group, and the C_{2-6} alkynyl group optionally are substituted with one or more substituents selected from the group consisting of: a halogen, an aryl group, a substituted aryl group, a heterocyclic group, a substituted heterocyclic group, -OR^6, -O-C_{1-6} alkyl group-R^6, -O-C_{2-6} alkenyl group-R^6, -O-C_{2-6} alkynyl group-R^6, and–NR^7R^8;

(ii) R^6 is selected from the group consisting of: hydrogen, an aryl group, a substituted aryl group, a heterocyclic group, and a substituted heterocyclic group;

(iii) R^7 and R^8 independently are selected from the group consisting of: hydrogen, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group,

wherein

the C_{1-6} alkyl group, the C_{2-6} alkenyl group, and the C_{2-6} alkynyl group are optionally substituted with one or more substituents selected from the group consisting of: halogen, an aryl group, a substituted aryl group, a heterocyclic group, a substituted heterocyclic group, $-OR^5$, and $-NR^9R^{10}$;

wherein

R^9 and R^{10} independently are selected from the group consisting of: hydrogen, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group; or

R^9 and R^{10} taken together with the nitrogen atom to which they are connected form a 3- to 7-membered ring, optionally containing one or more substituents selected from the group consisting of: –O–, –NH–, -N(C_{1-6} alkyl group) –, –N(aryl)–, –N(heteroaryl)–, –S–, -S(O)–, $-SO_2-$, and –C(O)–; or

R^7 and R^8 taken together with the nitrogen atom to which they are connected form a 3- to 7-membered ring, optionally containing one or more substituents selected from the group consisting of: –O–, –NH–, –N(C_{1-6} alkyl group) –, -N(aryl)–, -N(heteroaryl)–, –S–, -S(O)–, $-SO_2-$, and –C(O)–; and

(iv) G is selected from the group consisting of: –OC(O) –, -OC(O)O–, $-OC(O)NR^7-$, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)O-$, $-NR^7C(O)NR^8-$, $-NR^7C(NH)NR^8-$, -S-, –S(O)-, and $-SO_2-$;

(b) R^4 is selected from the group consisting of: hydrogen, a hydroxy protecting group, -C_{1-6} alkyl group–G–R^6, –C_{2-6} alkenyl–G–R^6, and –C_{2-6} alkynyl–G–R^6;

(c) R^5 is selected from the group consisting of: hydrogen, a hydroxy protecting group, R^6, -V-W-R^6, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group,

wherein

(i) V is -C(O)-, -C(O)O-, -C(O)NR^7-, or absent;

(ii) W is a C_{1-6} alkyl group, a C_{2-6} alkenyl group, C_{2-6} alkynyl group, or absent; and

(iii) the C_{1-6} alkyl group, the C_{2-6} alkenyl group, and the C_{2-6} alkynyl group are optionally substituted with one or more substituents selected from the group consisting of: a halogen, an aryl group, a substituted aryl group, a heteroaryl group, a substituted heteroaryl group, $-OR^6$, -O-C_{1-6} alkyl group-R^6, -O-C_{2-6} alkenyl group-R^6, -O-C_{2-6} alkynyl group-R^6, and $-NR^7R^8$;

(d) Q is selected from the group consisting of: $-NR^7CH_2-$, $-CH_2-NR^7-$, -C(O)–, -C(=NOR^6)–, –C(=N-NR^7R^8)–, -CH(-OR^6)–, and –CH(-NR^7R^8)–;

(e) J is selected from the group consisting of: $-CH_3$, $-CH_2CH_3$, -CH(OH)CH_3, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group;

wherein

the C_{1-6} alkyl group, the C_{2-6} alkenyl group; and the C_{2-6} alkynyl group optionally are substituted with one or more substituents selected from the group consisting of: an aryl group, a substituted aryl group, a heteroaryl group, and a substituted heteroaryl group;

(f) T is selected from the group consisting of: $-OR^5$, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, $-NR^7R^8$, –C(O)-R^6, –C(O)–C_{1-6} alkyl group-R^6, –C(O)–C_{2-6} alkenyl group-R^6, –C(O) –C_{2-6} alkynyl group-R^6,

wherein

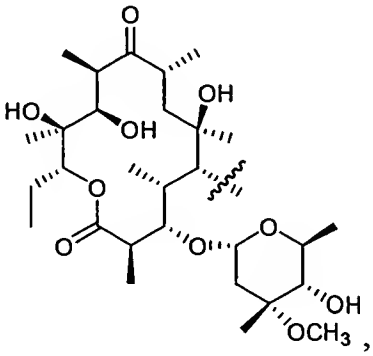
the C_{1-6} alkyl group, the C_{2-6} alkenyl group, and the C_{2-6} alkynyl group optionally are substituted with one or more substituents selected from the group consisting of: a halogen, an aryl group, a substituted aryl group, a heterocyclic group, a substituted heterocyclic group, $-OR^6$, –O–C_{1-6} alkyl group-R^6, -O-C_{2-6} alkenyl group–R^6, –O–C_{2-6} alkynyl group-R^6, and $-NR^7R^8$; and

Y is $-OR^5$; or

T and Y taken together with the atoms to which they are attached form a 5-membered ring by attachment to each other through a linker selected from the group consisting of: –OC(O)O–, –OC(O)NR^7–, -OC(S)O-, –OC(S)NR^7–, –OC(O)CHR^7–, and –OC(S)CHR^7; and

(g) Z is selected from the group consisting of: hydrogen, methyl, and a halogen.

3. The compound as in any one of claims 1 and 2 wherein M is selected from the group consisting of: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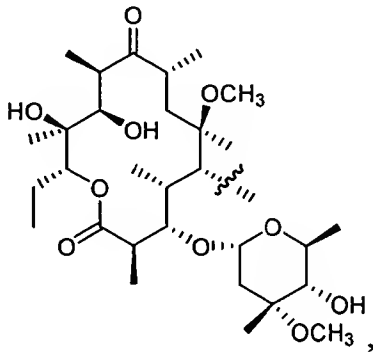
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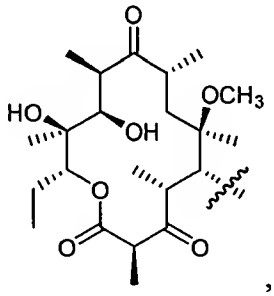
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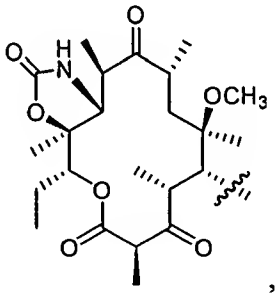
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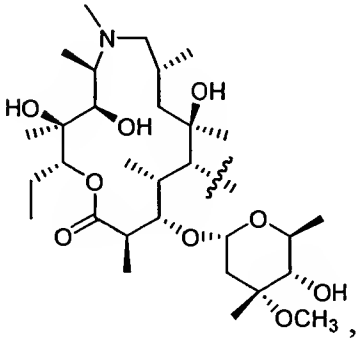
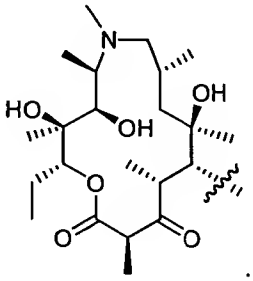
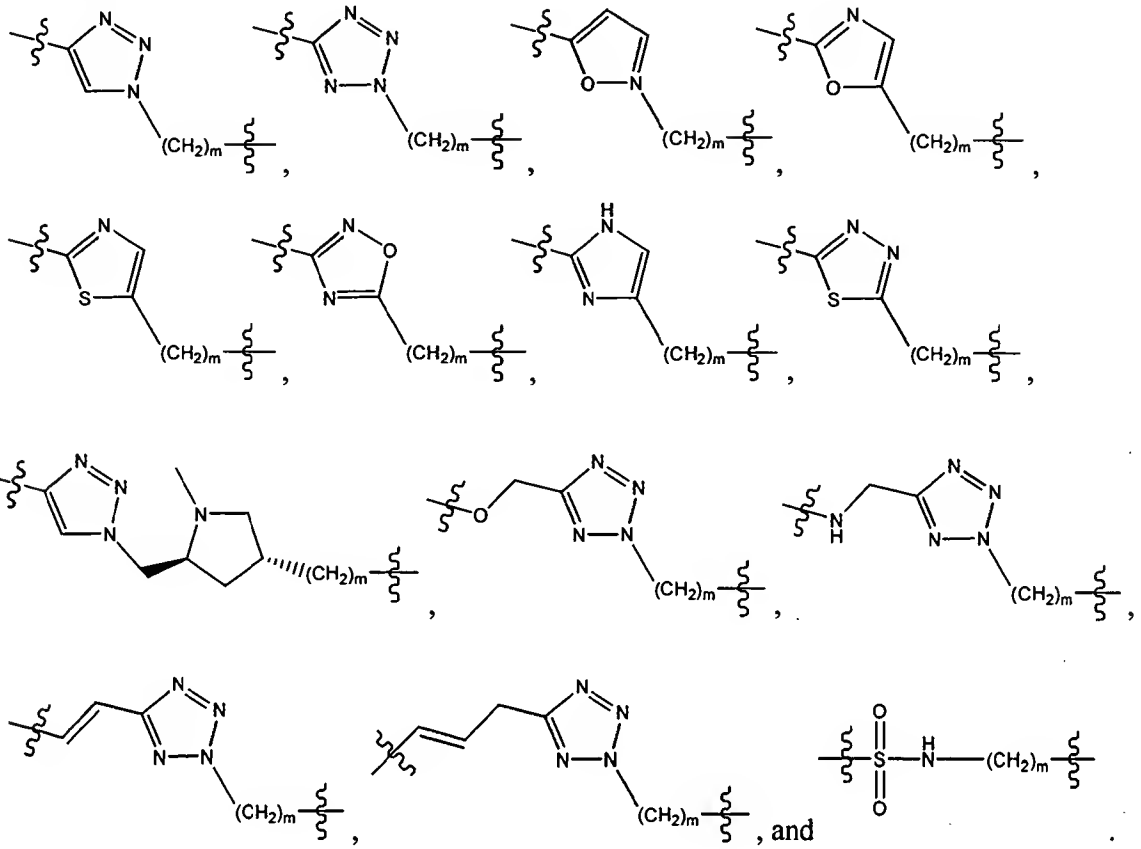
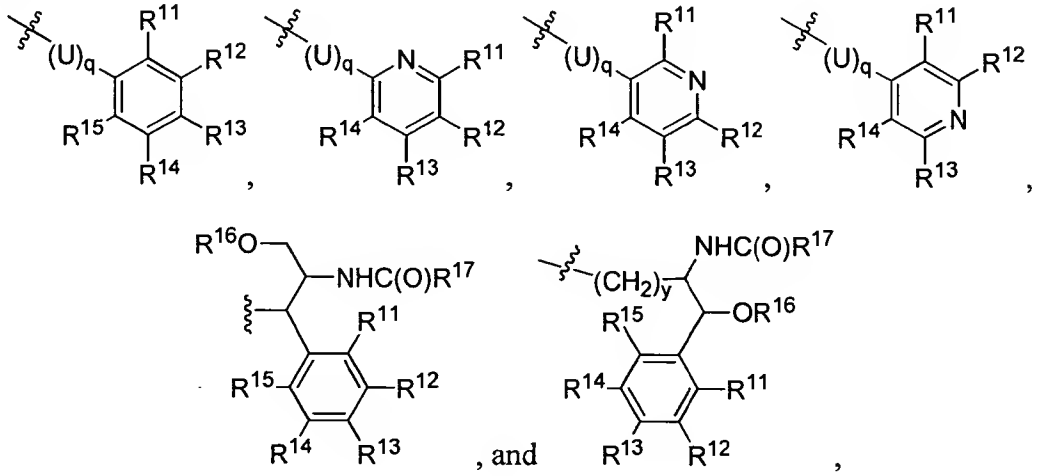

, and

.

4. The compound as in any one of claims 1-3 wherein L-$(CH_2)_m$ is selected from the group consisting of:



5. The compound as in any one of claims 1-4 wherein A is selected from the group consisting of:



wherein

R^{11}, R^{12}, R^{13}, R^{14}, and R^{15} independently are selected from the group consisting of: $-R^7$, $-OR^7$, $-NHC(O)R^7$, $-C(O)R^7$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-SO_2NR^7R^8$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NO_2$, -F, -Cl, -Br, -I, and a 5- or 6-membered saturated, unsaturated or aromatic heterocyclic ring containing one or more oxygen, nitrogen, and sulfur atoms,

wherein the 5- or 6-membered saturated, unsaturated or aromatic heterocyclic ring optionally is substituted with one or more chemical moieties selected from the group consisting of: $-R^7$, $-OR^7$, $-NHC(O)R^7$, $-C(O)R^7$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-SO_2NR^7R^8$, $-NR^7R^8$, $-C(O)NR^7R^8$, $-NO_2$, -F, -Cl, -Br, and -I;

R^{16} is hydrogen or a hydroxy protecting group;

R^{17} is methyl, a mono-halomethyl group, di-halomethyl group, or a tri-halomethyl group;

U is selected from the group consisting of: -O-, -NH-, $-NR^7-$, -S-, -S(O)-, $-SO_2-$, $-SO_2NH-$, $-SO_2NR^7-$, -C(O)-, -C(O)NH-, $-C(O)NR^7-$, -C(NOH)-, $-C(NOR^7)-$, and –C(S)-;

q is 0 or 1;

y is 0, 1, 2, or 3; and

R^7 and R^8 are as defined in claim 2.

6. The compound as in claim 5 wherein U is –O- and q is 1.

7. The compound as in any one of claims 1-6 wherein n is 1, 2, 3, or 4, and m is 0, 1, or 2.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of claims 1-7.

9. A method of treating a microbial infection in a mammal comprising administering to the mammal an effective amount of a compound as in any one of claims 1-7.

10. A method of treating a fungal infection in a mammal comprising administering to the mammal an effective amount of a compound as in any one of claims 1-7.

11. A method of treating a parasitic disease in a mammal comprising administering to the mammal an effective amount of a compound as in any one of claims 1-7.

12. A method of treating a proliferative disease in a mammal comprising administering to the mammal an effective amount of a compound as in any one of claims 1-7.

13. A method of treating a viral infection in a mammal comprising administering to the mammal an effective amount of a compound as in any one of claims 1-7.

14. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an effective amount of a compound as in any one of claims 1-7.

15. A method of treating a gastrointestinal motility disorder in a mammal comprising administering to the mammal an effective amount of a compound as in any one of claims 1-7.

16. The method as in any one of claims 9-15 wherein the compound is administered orally, parentally, or topically.

17. A method of synthesizing a compound as in any one of claims 1-7.

BIFUNCTIONAL HETEROCYCLIC DERIVATIVES AND METHODS OF MAKING AND USING THE SAME

ABSTRACT

The invention provides a family of bifunctional heterocyclic compounds useful as anti-infective and anti-proliferative agents. The invention also provides methods of making the bifunctional heterocyclic compounds, and methods of using such compounds as anti-infective and anti-proliferative agents.

3029836

APPLICATION DATA SHEET

Application Information

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Filing Date::	
Application Type::	Provisional
Subject Matter::	Utility
CD-ROM or CD-R?::	None
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Number of Copies of CDs::	
Sequence Submission?::	No
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Number of Copies of CRF::	
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Request for Non-Publication?::	No
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Total Drawing Sheets::	
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Contract or Grant Numbers::	
Secrecy Order in Parent Appl.?::	No

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